DOCUMENT RESUME

ED 290 250 EC 201 711

TITLE	Investigation of Alleged Scientific Misconduct on Grants MH-32206 and MH-37449. Final Report and Summary.
INSTITUTION	National Inst. of Mental Health (DHHS), Rockville, MD.
PUB DATE	28 Apr 87
NOTE	328p.; Portions of appendices contain marginally legible print.
PUB TYPE	Reports - Evaluative/Feasibility (142)
EDRS PRICE	MF01/PC14 Plus Postage.
DESCRIPTORS	*Drug Therapy; *Ethics; *Mental Retardation; *Research Methodology
IDENTIFIERS	*Bruening (Stephen)

ABSTRACT

The report presents results of a Department of Health and Human Services (DHHS) investigation into alleged scientific misconduct by Dr. Stephen Bruening in relation to two federally supported projects concerning tardive dyskinesia in retarded populations and stimulant drug use with mentally retarded children. The investigative panel of scientists unanimously concluded that Dr. Breuning knowingly, willfully, and repeatedly engaged in misleading and deceptive practices in reporting results of research, that he did not carry out the research, and that only a few of the experimental subjects described in publications were ever studied. The detailed report has sections on: investigation background, the panel formation and purpose, methods and process, research sites, panel findings, impact of the reported research on the field, conclusions, and recommendations. Most of the document consists of appendixes including the following: initial letter bringing the matter to DHHS attention; Bruening biographical material; individuals interviewed by the panel; sites visited by the panel; publications reviews by the panel and their analysis; and analyses of studies reported under the federal grant on stimulant drug use. (DB)

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DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Memorandum

Date April 28, 1987

From Acting Director, National Institute of Mental Health

Subject Investigation of Allegations of Scientific Misconduct under Grants MH-32206 and MH-37449

To Administrator, Alcohol, Drug Abuse, and Mental Health Administration

With this memorandum I am forwarding for your consideration and action the report and recommendations of a Panel of Senior Scientists established by this Institute to investigate allegations of scientific misconduct under the above-referenced grants. I accept the report and endorse the recommendations of the Panel.

Frank J Sullivan

Frank J. Sullivan, Ph.D.

Attachment

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Memorandum

Date · April 20, 1987

From Panel to Investigate Allegations of Scientific Misconduct under Grants MH-32206 and MH-37449

Subject Report and Recommendations of the Panel

To Acting Director, National Institute of Mental Health

On January 12, 1987, we sent you our report on our investigation of allegations of scientific misconduct under the above-referenced grants. We withheld our recommendations until comments had been received from the individuals and institutions indicated in the conclusions. We have received and considered those comments. The attached report now includes our response to the comments that were received and our recommendations regarding both the sanctions and other actions indicated and more general issues raised in the course of the investigation.

Attachment

Arnold J. Friedhoff

Arnold J. Friedhoff, M.D., Chairman
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FINAL REPORT

INVESTIGATION OF ALLEGED SCIENTIFIC MISCONDUCT

on

GRANTS MH-32206 and MH-37449

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I. Background and Purpose of the Investigation

On December 16, 1983, the National Institute of Mental Health (NIMH) Project Officer on grant MH-32206 received a telephone call from Dr. Robert L. Sprague, Director, Institute for Child Behavior and Development, University of Illinois at Urbana-Champaign, and Principal Investigator on that grant. Dr. Sprague expressed serious concern regarding data collected and published by Dr. Stephen E. Breuning, then Assistant Professor of Child Psychiatry, University of Pittsburgh. Dr. Breuning had been a consultant and collaborator on MH-32206 and was carrying out research, under subcontract, supported by Dr. Sprague's grant. Dr. Breuning was also Principal Investigator on grant MH-37449, "Stimulant Drug Use with Mentally Retarded Children," to the University of Pittsburgh, and he had submitted for review (and later withdrew) application MH-38184, "Drug/Behavior Therapy in Psychiatrically Ill Retarded."

Dr. Breuning, in the space of only a few years, had obtained considerable attention in the field of research on the mentally retarded.* Dr. Sprague said that he had been introduced to Dr. Breuning in 1978 by a colleague who had heard one of Dr. Breuning's presentations. Dr. Sprague was impressed by Dr. Breuning's abilities as an investigator and organizer. When Dr. Sprague had to move one field site of research on his rating scale for tardive dyskinesia from a facility in Illinois, he moved it to the Coldwater Regional Center, Coldwater, Michigan, where Dr. Breuning was then employed.

Stephen E. Breuning was born on September 18, 1952. He received his B.S. in psychology and biology in 1973, and his M.A. in psychology in 1974, from Western Michigan University, and his Ph.D. in psychology from the Illinois Institute of Technology in 1977.

His curriculum vitae (Appendix C) states that he was the Director of Behavioral Programs and Research, South Suburban Chicago Schools Project, Chicago, from March 1976 to December 1977. In June 1977, apparently prior to completing the position he reported with the Chicago schools, Dr. Breuning accepted a position as Psychologist at the Oakdale Regional Center for Developmental Disabilities in Lapeer, Michigan, and he held this position until September 1978. At that time he transferred to the Coldwater Regional Center for Developmental Disabilities in Coldwater, Michigan, where he was Psychologist and Research Director until he resigned in January 1981.

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* The term "mentally retarded" rather than "developmentally disabled" is used in this report because the former was used in grant applications and reports and studies reviewed by the Panel.

Dr. Breuning also held academic appointments. From 1979 to 1983, he was Adjunct Assistant Professor, Department of Psychology, Western Michigan University. In January 1981, he was appointed Assistant Professor of Child Psychiatry, Western Psychiatric Institute and Clinic (WPIC), School of Medicine, University of Pittsburgh. In June 1981, Dr. Breuning was appointed Acting Director and Director of Research for the John Merck Program, a part of WPIC. He held this position until his resignation on April 30, 1984. It is understood that he is currently employed as the Director of Psychological Services and Behavioral Treatment at the Polk Center in Polk, Pennsylvania. He has made appearances as an expert in the treatment of the mentally retarded.

Dr. Sprague followed his December 16, 1983, telephone call with a letter (Appendix A) detailing his concerns. He regarded much of the data reported by Dr. Breuning as unsupportable and provided in his letter two examples. The first concerned studies described in a progress report submitted by Dr. Breuning on grant MH-37449. Dr. Sprague felt it unlikely that the studies could have been conducted within the time period reported. The second example involved an abstract of a paper Dr. Breuning had intended to present at the December 1983 meeting of the American College of Neuropsychopharmacology. The abstract described a study using subjects from Dr. Breuning's previous place of employment, the Coldwater Regional Center. When raw data were requested by Dr. Sprague and by a coauthor of an earlier related paper, Dr. Breuning said that he could locate original data for only 24 of the 45 subjects reported.

Dr. Sprague had also conveyed his concerns to Dr. Theodore L. Brown, Vice Chancellor for Research and Dean, Graduate College, University of Illinois at Urbana-Champaign. On December 28, 1983, Dean Brown appointed a committee, chaired by the Associate Dean of the Graduate College, Elaine Copeland, to carry out an investigation. The committee was instructed to address three points:

1. Is there a reasonable basis for suspecting fraudulent scientific practice on the part of Dr. Breuning, with or without the possible complicity of other coworkers?

2. If the answer to this first question is yes, is there any evidence of complicity or willful participation in such fraudulent practice on the part of Dr. Sprague, or any other University of Illinois faculty or staff who have been associated with Dr. Breuning during the course of this research?

3. If the answer to the first question is yes, did Professor Sprague exercise reasonable diligence and take appropriate actions in notifying responsible officials at the University of Pittsburgh, NIMH, and elsewhere, of his findings and suspicions?

At the request of NIMH, the committee also considered whether Dr. Breuning's research results related to Dr. Sprague's work in such a way that, should they prove to be defective, they would adversely affect the value of Dr. Sprague's work.

On April 9, 1984, the committee reported (Appendix B) to Dean Brown that there appeared to be a reasonable basis for suspecting fraudulent scientific practice by Dr. Breuning; that there was no evidence of complicity or willful participation in such practice by Dr. Sprague or any other University of Illinois faculty or staff associated with Dr. Breuning during the course of the research; that Dr. Sprague had exercised reasonable diligence and taken appropriate action in notifying responsible officials of his concerns; that the data used in Dr. Sprague's research were independent of those of Dr. Breuning; that there was no evidence that Dr. Sprague's research conclusions had been affected by Dr. Breuning's data; and that the findings Dr. Breuning had reported had no impact on Dr. Sprague's work. The committee concluded that there was reasonable cause for a thorough investigation and assumed that it would be carried out by the University of Pittsburgh.

On January 17, 1984, NIMH had formally notified the University of Pittsburgh (Appendix B) of Dr. Sprague's concerns. Since telephone discussions with university officials had revealed that the university was already investigating the matter, NIMH indicated that it would wait for the report of the investigation before deciding on Institute action.

On February 8, 1984, the Chairman, Department of Psychiatry, University of Pittsburgh, notified NIMH that an informal investigation, conducted by three senior faculty members of the department, had disclosed inaccuracies in Dr. Breuning's report of the research design and followup data of the Coldwater study (Appendix B). In accordance with university policy, the Dean of the Medical School then appointed a committee of three tenured faculty from outside the Department of Psychiatry to gather information and report to him in writing. On February 17, that committee reported to the Dean that (1) studies performed at Coldwater over a period of 3½ years were unable to be supported by data; (2) based on inability to review raw data from the Coldwater study, a coauthor had retracted a paper submitted for publication; and (3) Dr. Breuning had withdrawn a NIH (NIMH) grant renewal application, claimed it was submitted mistakenly, and provided a revised copy he claimed should have been submitted. The committee stated it had not reviewed Dr. Breuning's work in Pittsburgh. Based on the noted irregularities, the committee recommended a formal investigation. On February 27, the Dean notified NIMH that a formal investigation was being undertaken.

On May 8, 1984, after receiving a copy of the report of the Department of Psychiatry's informal investigation, NIMH wrote the Dean:

> It would appear ... that initial inquiries have been limited to the research he conducted at Coldwater under grant MH-32206. ...We believe that the report of the Research Hearing Board should contain a review of all of Dr. Breuning's federally supported research activities at the University of Pittsburgh to determine the nature and full extent of any scientific misconduct which may have occurred.

Despite this request, on July 6 the university forwarded to NIMH the report of the hearing board which noted that because Dr. Breuning had resigned from the University of Pittsburgh, the scope of the board was "limited to determine if the research in question resulted in misuse of NIMH funds." The board reported:

> As a result of this review and of further information received..., the committee has unanimously concluded that the follow-up studies that were reported to have been carried out at Coldwater were not used as a basis for application or receipt of funds from NIMH. In addition, as best we can determine, the work in question did not significantly effect the conduct of other research carried out at the University of Pittsburgh or the expenditure of grant support which he received from NIMH. Thus, the committee has concluded that no misuse of funds occurred and that this matter should be closed.

An additional investigation was carried out by the University of Pittsburgh after this Panel began its work. In March 1985, in response to continued suggestions from NIMH, the Department of Psychiatry established an Ad Hoc Committee to assess Dr. Breuning's activities under grant MH-37449. The report of that group was sent to NIMH on May 10, 1985. The committee had exhaustively reviewed medical records of all inpatients admitted to the Merck unit during Dr. Breuning's tenure. It also reviewed pharmacy records and interviewed present and former staff. The committee concluded that data for the majority of subjects reported in Dr. Breuning's progress reports under MH-37449 could not be identified as studies conducted on the Merck unit. The full report of the Ad Hoc Committee is in Appendix B and is discussed more fully in Appendix J.

II. Formation of the Panel

On August 14, 1984, NIMH notified the University of Pittsburgh and Dr. Breuning that, because of unresolved issues, it would conduct a comprehensive investigation of allegations of scientific misconduct against Dr. Breuning.

The NIMH Investigative Panel was formally established in January 1985. The Panel was selected to include senior investigators with extensive experience in mental retardation, pharmacologic treatment, behavior analysis, and research design and methodology. One member was also a representative of the National Advisory Mental Health Council. The following are the members of the Panel:

Arnold J. Friedhoff, M.D., Chairman
Professor of Psychiatry and
Director of Millhauser Laboratories
New York University School of Medicine
New York, New York

C. Keith Conners, Ph.D.
Director of Research
Department of Psychiatry
Children's Hospital National Medical Center
Washington, D.C.

Richard I. Shader, M.D.
Professor and Chairman, Department of Psychiatry
Tufts University School of Medicine
Psychiatrist-in-Chief, New England Medical Center
Boston, Massachusetts
Member, National Advisory Mental Health Council

Herbert G. Vaughan, Jr., M.D.
Director, Rose F. Kennedy Center for Research
in Mental Retardation and Human Development
Professor of Neuroscience, Neurology and Pediatrics
Albert Einstein College of Medicine
New York, New York

Edward F. Zigler, Ph.D.
Sterling Professor
Department of Psychology
Yale University
New Haven, Connecticut

Public Health Service staff members who worked with, or consulted with, the Panel were:

Lorraine B. Torres
Director, Division of Extramural Activities, NIMH

Eugenia P. Broumas
Office of the Director, NIMH

Wright Williamson, M.S.W.
Division of Extramural Activities, NIMH

Joel M. Mangel
Deputy Associate General Counsel for Public Health
Department of Health and Human Services

Chris B. Pascal
Senior Attorney
Office of General Counsel, Public Health Division
Department of Health and Human Services

Consultant Investigator:

James Schriver

III. Charge to the Panel

The Institute's charge to the Investigative Panel was as follows:

> The Panel is to review the circumstances and events related to the allegation of scientific misconduct against Stephen E. Breuning.
>
> The Panel is asked to:
>
> determine if scientific misconduct has occurred and, if so, to describe its nature, extent, and seriousness
>
> identify, if such misconduct is substantiated, any or all individuals who participated in the alleged or other misconduct
>
> identify NIMH, or other PHS, support instruments and awards that were involved
>
> recommend any actions or sanctions that appear to be indicated and prudent to deal with the described circumstances

IV. Public Health Service Grants Involved

The following Public Health Service (PHS) grants were for work by Dr. Breuning, involved his participation, or were cited by him in publications or manuscripts:

R01 MH-32206
University of Illinois at Urbana-Champaign
Robert L. Sprague, Ph.D., Principal Investigator
Assessing Tardive Dyskinesia in Retarded Populations

This grant began January 1, 1979, and is still active. Its objectives were stated in the original application as (1) to develop and refine behavioral monitoring procedures to assist State institutions and community facilities to comply with court orders and State law and regulations regarding use of psychotropic drugs in the treatment of the mentally retarded; and (2) to conduct experimental studies on various parameters (with dosage as the first) on the use of psychotropic drugs with this population. The study was to be carried out at three Illinois institutions for the developmentally disabled. Dr. Breuning was not named in the initial application.

During the first grant year, Dr. Sprague notified the NIMH project officer that it had become impossible for him to carry out the proposed research at institutions in Illinois, and he requested and received permission to substitute for one study site the Coldwater Regional Center for Developmental Disabilities (CRC), Coldwater, Michigan.

In his interview with the Panel, Dr. Breuning minimized his relation to this grant. However, in a document sent to the Coldwater Administrator, Robert Rogan, dated December 3, 1979, Dr. Breuning defined his relation to the grant. He listed himself as Research and Training Supervisor/Coordinator of the Behavioral Pharmacology and Mental Retardation Research and Training Program. He described the program as follows:

> The Behavioral Pharmacology and Mental Retardation Research and Training Program is an interagency program concerned with all aspects of drug use with the mentally retarded. The Program has been approved by the Michigan Department of Mental Health and receives financial support through grant MH-32206 from the National Institute of Mental Health to Dr. Robert L. Sprague, Director of the Institute for Child Behavior and Development at the University of Illinois-Champaign/Urbana.

In the progress report submitted by Dr. Sprague at the end of the first year, a number of studies at Coldwater were reported, including revision of the Resident Behavior Rating Scale (RBRS) and arrangements for its use on several residents in each of the six living units; work almost completing a Dyskinesia Rating Scale for Developmentally Disabled and training staff in its use; making of a training videotape of a resident with moderate dyskinesia; and assessment on a matching-to-sample task of 12 subjects who had received simple psychoactive medication. The progress report described Dr. Breuning's role as follows:

> Dr. Breuning is our consultant and liaison at Coldwater Regional Center. He will supervise all research done in conjunction with our project (such as Wysocki's dissertation research) and is our on-site "trouble shooter" should any problems arise requiring immediate attention. Dr. Breuning's value to our project extends far beyond his consultant role, and includes formal, but nonetheless vital, contact with members of administrative and professional staffs, as well as effective encouragement of qualified personnel to engage in related studies involving drug reduction and withdrawal with chronically-medicated residents. His services to the project are provided by Coldwater Regional Center at no salary cost to the project.

Dr. Sprague also reported that Ms. Vicky Davis, formerly a staff psychologist at the Coldwater Regional Center, had been appointed on September 10, 1979, as a project staff member spending 75 percent time. Her salary was paid directly by the University of Illinois from grant funds. With NIMH project officer permission, grant funds were also used to pay tuition for her courses at Western Michigan University where she was enrolled in a Master's program.

On May 30, 1980, Dr. Sprague submitted renewal application 2 R01 MH-32206-03. Dr. Breuning was listed as a consultant and Ms. Vicky Davis as a full-time project staff member to be paid from grant funds. Work at Coldwater was reported in the progress section, and further work there was an integral part of the proposal. Dr. Breuning was present in Urbana-Champaign when the project was site visited on November 4, 1980, by members of the NIMH Treatment Development and Assessment Review Committee. Work at the center was considered by the committee in its assessment which led to an award for 3 years of further support.

In the progress report on the third grant year, submitted January 26, 1982, three publications of Dr. Breuning's were listed as published, and two more were listed as in press. Work at the center was described by Dr. Sprague:

> Although some survey data were collected at Coldwater Regional Center for Developmental Disabilities, Coldwater, Michigan, the instruments were less inclusive, drug histories were for a shorter period and less inclusive, and the DIS-Co (Dyskinesia Identification System-Coldwater) raters received no formal training. Therefore, the data were not considered comparable with the data from the Minnesota surveys, and they will not be included in the larger data pool.

Dr. Sprague continued to report Dr. Breuning's publications in his progress reports.

Dr. Breuning left Coldwater in December 1980, and was appointed Assistant Professor of Child Psychiatry, Western Psychiatric Institute and Clinic (WPIC), University of Pittsburgh, in January 1981. During the third grant year, a subcontract under MH-32206 was awarded to the University of Pittsburgh to continue Dr. Breuning's collaboration. On May 29, 1981, Dr. Sprague submitted an application for supplemental funds for subcontracts with the University of Pittsburgh for 2 more years. The purpose of the supplements, as described, was to include mentally retarded children, ages 3-12, in the John Merck Program, WPIC, in "all aspects of the current grant," including "evaluation of dyskinesia, statistical properties of the DIS-Co and RBRS, and effects of psychotropic drugs on various measures of performance. A controlled thioridazine study will be conducted." The supplemental funds were approved and awarded for the 4th and 5th years of the grant (Appendix K). Audited charges of $55,192.12 were made and a total of $51,333.03 was paid to the University of Pittsburgh over 3 years. Final settlement of accounts between the Universities of Illinois and Pittsburgh is pending the outcome of this investigation.

On June 14, 1983, Dr. Sprague submitted a renewal application for 5 additional years of support. Dr. Breuning was listed as a Co-Principal Investigator. The University of Pittsburgh was to be one of four sites of proposed research. Specific aims for Pittsburgh were: to continue examining the effects of naturally occurring medication and dosage changes on observed target behavior; to plan and conduct a prospective study of thioridazine and haloperidol in responders and nonresponders, using dose of medication as the major experimental variable; to develop and test a stereotypy rating scale; and to investigate the effects of different environments (e.g., setting, structure, and time of day) on the stereotypy and DIS-Co scales in order to enhance differential diagnosis of the two conditions. Proposed effort and requested salary support for Pittsburgh staff were: Dr. Breuning, 20 percent effort, 10 percent salary; Rowland P. Barrett and Edward J. Nuffield, 5 percent effort and salary for both; Patrick K. Ackles, 10 percent effort, no salary; Sue Ann Fultz, 100 percent effort and salary; Vicky Davis, 35 percent effort and salary.

In the progress section, 21 publications on which Dr. Breuning was author or coauthor were listed as appearing since the last review, 5 more were listed as in press, and 2 were listed as in manuscript.

The initial scientific review committee recommended 1 year of support at a reduced level for reanalysis of already collected data to revise the DIS-Co. The committee noted that the proposed work at Pittsburgh raised interesting questions but seemed unrelated to the major aim of Dr. Sprague's work and should perhaps be the subject of a separate application. The award for a 6th year of support included no funds for work by Dr. Breuning.

R01 MH-37449
University of Pittsburgh
Stephen E. Breuning, Ph.D., Principal Investigator
Stimulant Drug Use with Mentally Retarded Children

Application MH/HD-37449-01, "Stimulant Drug Use with Mentally Retarded Children," from the University of Pittsburgh, with Dr. Breuning as Principal Investigator, was received by NIMH on October 1, 1981. In it Dr. Breuning proposed to examine appropriate dose levels of stimulant drugs - methylphenidate and dextroamphetamine - in the treatment of 48 hyperactive mentally retarded children served by the Psychiatric Service for Multiply Handicapped Children (John Merck Program), WPIC. Dr. Breuning was to devote 20 percent of his time to the project, with 15 percent salary support requested. His duties were described as being responsible for overall coordination and administration of the project, including supervision of project staff, monitoring the assessment and treatment phases of the study, overseeing data analysis, and preparing all resulting manuscripts and reports.

The application was reviewed by an NIMH initial review group in February 1982, and by the National Advisory Mental Health Council in May 1982. It was recommended for approval for 2 years, and awards were made for July 1, 1982, through June 30, 1984, for a total amount of $133,047. At the request of the University of Pittsburgh, it was terminated March 31, 1984.

On April 29, 1983, in a progress report to NIMH, Dr. Breuning reported that just over 65 percent of the children for the methylphenidate studies and approximately 35 percent of those for the dextroamphetamine studies had completed the protocol. Three studies were described. Two publications in press and one submitted for publication were listed.

A competing continuation application, for 4 additional years of support, was received October 1, 1983. In it Dr. Breuning described six studies and about 65 percent of a seventh study as completed. Eleven publications were listed as published, in press, or in preparation. This application was withdrawn by Dr. Breuning on December 12, 1983. As noted above, a University of Pittsburgh Ad Hoc Committee reported on May 10, 1985, that the subjects reported could not have been on the John Merck Program. When Dr. Breuning met with the Panel on November 22, 1985, he told the Panel that he had not conducted any of the reported work at Pittsburgh. Dr. Breuning's reports and his activities under this grant are discussed in Section VII, and in detail at Appendix J.

P50 30915
University of Pittsburgh
David J. Kupfer, M.D., Principal Investigator
Clinical Research Center for the Study of Affective
Disorders

Although cited by Dr. Breuning in a publication, a careful review of official records indicated that Dr. Breuning received no direct support from this grant but may have made use of general resources provided through the center.

Another application, 1 R01 MH-38184-01A1, "Drug/Behavior Therapy in Psychiatrically Ill Retarded," with Dr. Breuning as Principal Investigator, was submitted from the University of Pittsburgh on June 29, 1983, but was withdrawn before review. It was not considered by the Panel.

V. Methods and Process of the Investigation

From the time it received its charge and planned its investigation, the Panel proceeded in a careful and considered fashion. All Panel members received, reviewed, and commented on basic documents, including all studies, publications, and reports used.

Official files of NIMH were scrutinized, including grant applications, progress reports, financial reports, and related materials.

All articles and manuscripts citing PHS grant support and studies cited in grant progress reports were identified (Appendix H) and analyzed (Appendices I and J). Additional documents relating to significant aspects of the investigation were analyzed and are included in the detailed discussion.

At least two Panel members personally interviewed all of Dr. Breuning's major coauthors of the above articles who could be located. Additional materials were requested and received from several of them. Those interviewed were: Patrick Ackles, Salvatore Cullari, Neal A. Davidson, Vicky Davis, Donald G. Ferguson, C. Thomas Gualtieri, Johnny L. Matson, Alan D. Poling, and Lori Sisson.

The Panel interviewed Dr. Robert Sprague and received additional material from him.

The Panel, staff, or a consultant investigator contacted by letter, telephone, or in person a number of individuals for information relating to the investigation. Complete lists are appended at D and F.

When the Panel began its work, it operated on an assumption derived from grant applications, progress reports, and published material that the research in question had been carried out at the University of Pittsburgh or at the Coldwater Regional Center for Developmental Disabilities. As the Panel proceeded, it received conflicting information about possible research sites, specifically the Oakdale Regional Center and various schools and institutions in the Chicago area. It therefore broadened its inquiry.

Two Panel members and an NIMH staff member visited the Coldwater Regional Center for Developmental Disabilities, Coldwater, Michigan. Administrative and clinical staff were interviewed, administrative and clinical records examined, and clinical and research facilities inspected. Ancillary facilities, thought to be the location of some reported research, were also visited.

The entire Panel and NIMH staff visited the Western Psychiatric Institute and Clinic, University of Pittsburgh. University officials, coworkers of Dr. Breuning, members of the university investigative committees, and others were interviewed. Research facilities were inspected. Administrative, investigative, clinical, research, and pharmacy records were examined. Additional visits were made to the university by the Panel Chairman, NIMH staff, and a consultant investigator to the Panel.

A consultant investigator to the Panel visited the Oakdale Regional Center for Developmental Disabilities, Lapeer, Michigan, interviewed administrative and professional staff there, and reviewed administrative, research, and clinical records. Additional information from Oakdale staff was obtained by telephone interviews conducted by the Panel Chairman and/or NIMH staff.

Individuals named by Dr. Breuning as knowing about his work in the Chicago area were contacted by telephone by the Panel Chairman and NIMH staff.

The Panel and NIMH staff met with Ms. Vicky Davis, coworker of Dr. Breuning at Oakdale, Coldwater, and Pittsburgh, and with Dr. Breuning for extensive interviews. A verbatim transcript of the interview with Dr. Breuning was made available to him, and he was also invited to respond to written interrogations and to comment on this report in draft.

The Panel met nine times:

March 12, 1985
April 18-19, 1985
June 25-6, 1985
October 16, 1985
November 22, 1985
December 6, 1985
March 25, 1986
December 1, 1986
April 20, 1987

Additional meetings were held by staff with individual members of the Panel.

The following represents, therefore, the considered judgment of the Panel based on an intensive and extensive investigation. Because of the number of studies, coauthors, and possible research sites, the remaining sections of the report discuss first the possible research sites and present the Panel's summary findings. Detailed analyses of studies and findings on each are appended at I and J.

VI. Possible Research Sites

The site of the research reported was specifically identified in only two of the publications reviewed by the Panel, the Coldwater Regional Center, in Gualtieri, Breuning, Schroeder, and Quade (1982), and in Ferguson, Cullari, Davidson, and Breuning (1982). When the Panel began its work, it assumed, as noted previously, that the remaining studies were carried out at either Coldwater or the University of Pittsburgh, Dr. Breuning's places of employment between 1978-84, the period when the publications were prepared and when they appeared. As the Panel interviewed Dr. Breuning's coauthors and coworkers, and Dr. Breuning himself, the University of Pittsburgh, the Coldwater Center for Developmental Disabilities, Coldwater, Michigan; the Oakdale Regional Center for Developmental Disabilities, Lapeer, Michigan; schools in the Chicago area; and "various sites in Illinois" were identified, frequently contradictorily, as research sites. The detailed analyses of individual studies (Appendices I and J) include information about the possible site(s) of each study. The following is a brief description of each site.

University of Pittsburgh

In January 1981, Dr. Breuning moved to the Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine, as Assistant Professor of Child Psychiatry. In June 1981, he was appointed Acting Director/Research Director, John Merck Program for Multiply Disabled Children. He held these positions until he resigned from the university. He also had an appointment as Assistant Professor in the School of Education. From April 1, 1982, he attributed 10 percent of his time to activities related to Dr. Sprague's grant, MH-32206, and funded by subcontract with the University of Illinois. Grant MH-37449, on which he was Principal Investigator, was awarded July 1, 1982. Dr. Breuning attributed 20 percent of his time to research under that grant. On October 1, 1982, the Department of Education awarded a contract to the Early Childhood Research Institute, Western Psychiatric Institute and Clinic, on which Dr. Breuning was a co-investigator responsible for studies of disruptive behavior. He attributed 20 percent of his time to these studies. Overall, university administrators estimate that, while at Pittsburgh, Dr. Breuning spent 40 percent of his time in research, 10 percent in teaching, and 50 percent in clinical and administrative responsibilities.

The John Merck Program occupies the sixth floor, an area of approximately 11,000 square feet, of the Western Psychiatric Institute and Clinic. It is a 24-bed inpatient unit with an outpatient program. The sixth floor unit, visited by the Panel, includes living and play areas for the children, staff offices, several small classrooms, and two small treatment rooms used for academic and laboratory performance testing. Each of these rooms is equipped with either a one-way observation window or mirror. Matching-to-sample equipment was located in one of these rooms during Dr. Breuning's tenure. According to several persons interviewed and Dr. Breuning, fixed ratio equipment was present but never operational.

During the period Dr. Breuning was with the Merck Program, the staff consisted of six psychologists, three psychiatrists, four social workers, ten special therapists, five research associates, twenty nurses, and twenty child care workers. In addition, the Merck Program served as a rotation for pre- and post-doctoral psychology students, psychiatry residents, and psychiatry clerks who were enrolled in either the Department of Psychology or the School of Medicine.

Children treated by the program were ages 3-14, and an occasional older adolescent, with borderline to profound retardation and/or severe withdrawal associated with psychosis of some years' duration. Between July 1, 1980, and June 30, 1984, 278 inpatients were admitted to the Merck Program. A search of medical and pharmacy records by the University of Pittsburgh Ad Hoc Committee indicated only 11 received stimulant/placebo trials and matching-to-sample testing and were even possible subjects of Dr. Breuning's NIMH-supported research; only 5 of the 11 had discharge diagnoses meeting the criteria of that protocol.

Coworkers of Dr. Breuning in the Merck Program described weekly senior staff meetings. Decisions were made at those meetings to include children in studies. Participants included the head nurse, the chief social worker, the program's medical director, and Dr. Breuning. Those interviewed also indicated that there was no protocol and little distinction between research and clinical work. Physicians on the unit wrote the medication orders and obtained informed consents. The senior research assistant ordered and scheduled matching-to-sample testing. All children on the unit who were able to use the apparatus were tested three times a week, with a few tested five times. Tests were usually scheduled for the testers' convenience; only a few requests for specifically timed tests were made. All children on the unit appear to have been rated on the DIS-Co and the RBRS. Testing results were given to Dr. Breuning and entered in files which were also given to him when the child was discharged. When Dr. Breuning resigned from the University of Pittsburgh on April 30, 1984, he took this data with him.

Coldwater Regional Center

The Coldwater Regional Center for Developmental Disabilities, Coldwater, Michigan, was a residential facility for the mentally retarded and developmentally disabled during Dr. Breuning's employment there from September 1978 to January 1981. The center, operated by the Michigan State Department of Mental Health, served about 650 residents, 85-90 percent of whom were evaluated as severely or profoundly retarded. Residents were housed in individual buildings with a capacity of 40-50 beds each or in several larger dormitory-like buildings with 60-90 beds each. Six to nine teams, each consisting of a physician, psychologist, registered nurse, and licensed practical nurse provided diagnostic, assessment, and treatment services. Staff physicians did complete physical examinations on admission which, the Panel was told, could have included standard neurological workups. Residents requiring more specialized neurological assessment were sent to Ann Arbor. Special educational and vocational services were provided at the adjacent Evergreen School, Branch Intermediate School District. The center has since been scheduled to be turned into a facility for the chronically mentally ill. By October 1985, all but 54 severely ill residents were to have been placed in community facilities.

Dr. Breuning was assigned as psychologist to Building 42 which had about 70 residents ranging in age from 10 to 26. His primary role was to provide psychological services and develop programs for residents of Building 42. Research activities were considered peripheral to his primary responsibilities and not an integral part of his work. Dr. Neal Davidson, Director of Psychological Services, emphasized to the Panel that the center was primarily a residential facility and that little or no research was conducted at Coldwater before or after Dr. Breuning's employment there. Nevertheless, the Panel was told by several of Dr. Breuning's colleagues there that he had been a catalyst for research activities; that several of the psychologists at the center had interests similar to those of Dr. Breuning; and that time was made available for them to pursue those interests. A research committee was set up to review and pass on all proposed studies and papers to be presented or published by center staff. Dr. Breuning served on that committee. The Center Director, Mr. Robert L. Rogan, presented Dr. Breuning's proposed collaboration with Dr. Sprague to the State Department of Mental Health and on August 15, 1979, received the permission of the department to proceed with that research. Documents submitted by Dr. Breuning included Dr. Sprague's protocol, with the modification that medication would not be manipulated.

Policy in force at Coldwater at that time reflected the State's concern about objective review of psychotropic drugs and the reduction of medication with the mentally retarded population. Medication reduction was not submitted to the research committee, nor were informed consents sought for such reduction since it reflected treatment policy. Orders for medication reduction were written by staff physicians. The physician assigned to Building 42 at that time was Dr. Carlos Budding who has since returned to Argentina. Center officials told the Panel that placebo/double-blind procedures were not used there and it was not their practice to give placebos. The Panel received information and evidence that this was not always so. Dr. Breuning told the Panel that placebos, similar in appearance but not matched to medication, were used; that early on they were made up on his unit and not ordered through the pharmacy; that he thought they had bought the capsules at a supply house in Chicago and had a giant bag of them; and that he knew of no rules he had violated. He insisted that drug reduction was always ordered by a physician. He did say that placebos were administered without a specific physician's order, but he said that a physician was always aware of what they were doing. Dr. Cullari confirmed that placebos were used at Coldwater. He said that Dr. Breuning had one patient on placebos. The Panel found documentation of placebo administration in records of a treatment team to which Dr. Ferguson was assigned.

Building 42 had a room with a one-way observation window. It also had matching-to-sample equipment for testing and assessing the effects of tardive dyskinesia. Clients, ages 10-26, participated in educational and vocational projects at the Evergreen School where the workshop performance program included the Bendix bicycle brake assembly project. Behavioral observations were recorded routinely on a standard form by school staff. Dr. Breuning had access to and made use of school records. He also had and made use of access to medical records of Coldwater residents. A random review of patients' charts by the Panel indicated that behavioral observations were reported carefully and frequently on a 24-hour basis. Intervals between recorded observations varied. Reviewed records were from all buildings, including 42, and included some psychological assessments conducted by Dr. Breuning and some proposed treatment plans. A few of the records included DIS-Co ratings, consent forms for video taping, and doctors' orders for medication. The Panel established that, while assigned to Building 42, Dr. Breuning had access to residents of other buildings and some residents of other buildings were sent to him for testing.

Oakdale Regional Center

The Oakdale Regional Center for Developmental Disabilities, Lapeer, Michigan, was the site of Dr. Breuning's first professional employment following graduation in May 1977 from the doctoral program at the Illinois Institute of Technology. He was employed as a psychologist from June 10, 1977, until he transferred to Coldwater on September 18, 1978.

Dr. Breuning was assigned to Building 34E where he had responsibility for clinical services to residents, including testing, assessment, diagnosis, and treatment. Records of Building 34E for the period show 12 male residents, ages 27-59, and 45 female residents, ages 27-77. Staff said that most of the male patients were visually impaired and that many of the female patients displayed maladaptive behavior which required their participation in structured, programmed activities. Many required assistance in all areas of self-care, including ambulation.

Although hired as a clinical psychologist, Dr. Breuning's position description required that he prepare a proposal for psychological research. A note dated December 10, 1977, on his Probationary Service Record stated that he was relieved of this requirement "due to the weight of clinical duties in 34E."

At the time of his employment, Dr. Breuning was given permission to continue his research in the area of his dissertation, "Classical Conditioning in Goldfish." Space was provided, and he engaged in these studies with a colleague, Dr. John Regan, who had been a fellow graduate student at the Illinois Institute of Technology.

Policy at Oakdale required that all research proposals be reviewed by the research committee. Dr. Breuning was a member of that committee from August 19, 1977. Records of the committee show the following proposals submitted to the committee and the actions on them: On November 21, 1977, Dr. Breuning's proposed study, "Effects of Individualized Incentive on Norm-Referenced IQ Test Performance of Institutionalized Severe and Profound Adult Retardates," was distributed to the committee. A discussion was scheduled for December 5; however, Dr. Breuning was absent then, and the proposal was set aside and not brought up again. On September 26, the committee had considered a similar study from Jody R. Lewis, "The Effects of Reinforcement Procedures on the IQ Scores of Institutionalized Severe and Profound Retardates." Dr. Breuning had been present for that discussion. This study was Ms. Lewis' Master's thesis. She told Panel staff that Dr. Breuning had helped her design it.

Ms. Lewis was coauthor with Dr. Breuning and Vicky Davis on "Examination of Methods of Selecting Goal-directed Activities for Institutionalized Retarded Adults," in Education and Training of the Mentally Retarded, February 1981, pp. 5-12. Ms. Lewis said she had done a literature search and prepared a section of the article from data Dr. Breuning had previously collected, presumably in Illinois. She also participated in a presentation of the article at a poster session at the meeting of the Midwestern Association of Behavior Analysis, Chicago, on May 13-16, 1978. At those poster presentations, 14 studies from Oakdale were presented. Dr. Breuning was named first author or coauthor on 8 studies. Oakdale staff reported that, when they asked Dr. Breuning about the origin of the data for his poster presentations, he said he had gathered it prior to coming to Oakdale. Only one of the studies presented had been approved by the Research Committee. It was a summary report, "Successive Contrast Effects and Reduced Intersubject Response Variability in Appetitive Activity Conditioning with Goldfish," presented by Dr. Breuning on April 17, 1978, to the committee, The committee recommended that it be submitted for publication. On June 1, 1978, the committee reviewed a proposal by Drs. Breuning and Regan, "Brain Research With Goldfish: Anesthesiology and Histological Assessments"; and on September 5, publication was approved of "Classical Conditioning of Muricide Elicited From the Lateral Hypothalmus in Rats," by Drs. Breuning, Regan, and David A. Nolling. Records at Oakdale show that no requests from Dr. Breuning for research with human subjects were approved. Those of his colleagues and supervisors who were contacted were unanimous in their view that he had not, and could not have, conducted research with human subjects as reported in the studies attributed by him to Oakdale.

Chicago

Dr. Breuning's curriculum vitae indicates he was a graduate student and held various positions in the Chicago area between September 1974 and June (or December) 1977. The positions are described on page 1 of this report. In June 1977 he was appointed to the Oakdale Regional Center, Lapeer, Michigan. His curriculum vitae shows him also as a Director of Behavioral Programs and Research of the South Suburban Chicago Schools project to December of that year.

Dr. Breuning told the Panel that the work described in his progress reports on grant MH-37449, awarded for work at the University of Pittsburgh, was actually carried out in Chicago area schools almost 10 years before (Appendix J). He also attributed parts of several other studies (Appendix I) to the Chicago area. He maintained that he had attached himself to studies in progress. He could recall neither the names of the investigator(s) nor the name or location of any school or institution where he had gathered data. When asked by the Panel about drug manipulation and informed consent, Dr. Breuning replied that they had been the responsibility of the original investigator(s). Regarding his detailed descriptions of experimental room size and experimental apparatus, he replied that he had found rooms very similar in size and he had carried portable apparatus with him. A data book he provided to the Panel had no identifying material of any kind, including dates.

Dr. Breuning referred the Panel to two persons who could verify his having done such work in the Chicago area, Dr. John Regan, a former graduate student with Dr. Breuning at Illinois Institute of Technology and coworker for several months at Oakdale, and Dr. Paul Koutnik. Dr. Regan said he knew of no such work done by Dr. Breuning. Dr. Koutnik, an academic advisor at the Illinois Institute of Technology, who according to Dr. Breuning, had arranged for him to conduct research in Chicago area schools, stated that he was Associate Professor of Education at the Illinois Institute of Technology and that he served on Dr. Breuning's doctoral dissertation committee. During that period, he had arranged for Dr. Breuning to serve as a student teacher for 1 year in the Bloom Township, Illinois, High School where he taught sophomore biology and conducted workshops for teachers on classroom behavior management. Dr. Koutnik said, however, that he knew nothing of any research by Dr. Breuning involving human subjects and that he had not been involved in arranging for Dr. Breuning to conduct such research.

The Chairman of the Department of Psychology, Illinois Institute of Technology, and Dr. Breuning's doctoral dissertation advisor during the period in which Dr. Breuning stated he conducted the studies in the Chicago area, Dr. Alan Wolach, said that he knew nothing about research in the school system but that Dr. Breuning might not have mentioned this to him inasmuch as Dr. Breuning was expected to devote all of his research time to his dissertation research.

VII. Panel Findings

The Panel reviewed articles and manuscripts related to PHS grant support and grant progress reports and interviewed major coauthors. It site visited Coldwater and the University of Pittsburgh; interviewed officials, administrators, coworkers of Dr. Breuning, and other staff; and reviewed administrative, medical, and other records. The Panel interviewed and corresponded with Dr. Breuning. Panel staff and a consultant investigator interviewed other individuals and visited Oakdale. Based on this extensive and intensive investigation, the Panel has the following findings. (Because both possible sites and dates of much of the reported work are unclear, this section is organized by groups of studies addressing similar issues. Detailed descriptions, analyses, and findings for individual studies are at Appendices I and J.)

Dyskinesia Studies

Breuning, Ferguson, and Cullari (1980 and 1981) reported a study of dyskinesia and inappropriate behaviors in 10 institutionalized, young adult, mentally retarded subjects withdrawn from neuroleptics. An elaborate experimental design was involved, including placebo administration, extensive behavioral observations over a 28-week period, and the use of trained observers. As all three authors were at Coldwater when the article appeared, it could be assumed that the research had been carried out there. Dr. Breuning told the Panel that the research was carried out at Coldwater and Oakdale. His Coldwater coauthors, who did not see any raw data, said they thought the work had been done at Oakdale.

As part of his collaboration with Dr. Sprague, Dr. Breuning had proposed to study the effects of neuroleptics, and their withdrawal, on performance and behavior of Coldwater residents. It was policy in the State of Michigan and at Coldwater while Dr. Breuning was there to reduce or withdraw medication when possible. The Panel found evidence in patient records that some behavioral observations of residents were made, and it received information from Dr. Breuning that placebos were administered by him. However, Dr. Breuning produced no raw data for these studies, and, despite extensive questioning of the center director, the chairperson of the center research committee, the nurse, and other staff who worked with Dr. Breuning at Coldwater, no evidence could be found that deliberate drug manipulation according to a protocol, or administration of a placebo as described, was ever carried out there. There is no record at Oakdale of Dr. Breuning's having conducted research with human subjects there. His supervisors and colleagues at Oakdale were adamant that he could not have carried out such research.

Gualtieri, Breuning, Schroeder, and Quade (1982) reported a study of 57 subjects, early adolescent to elderly, from Coldwater, withdrawn from a neuroleptic treatment and assessed during withdrawal and for 80 weeks afterwards for dyskinesia. An abstract of an intended presentation by Dr. Breuning to the 1983 meeting of the American College of Neuropsychopharmacology (ACNP) reported an additional 2-year followup of 45 of the subjects. Gualtieri and Breuning (1983) reported on 8 of these subjects, early adolescent to young adult, who exhibited "withdrawal dysbehavior," a behavioral analog of dyskinesia.

The validity of this study was first questioned in late 1983 when Dr. Sprague raised questions as to whether Dr. Breuning could have carried out the study as described by Dr. Breuning in the ACNP abstract. In response, Dr. Breuning attempted to revise the abstract to show only one additional assessment, at 4 months, on only 24 subjects. When questioned by Dr. Sprague and his coauthor, Dr. Gualtieri, Dr. Breuning was unable to produce raw data or subject identifiers for the study proper. He provided some summary data and "raw data" for one assessment of 24 subjects at week 96. Dr. Breuning told the Panel that he collected some of the data for this study at Oakdale and that followup data on the 45 subjects were not systematically collected but were casual data collected by a nurse at Coldwater after he, Breuning, had left. He would not identify the nurse to the Panel.

As indicated above, the Panel found no evidence that such research could have been carried out at Oakdale. It did find evidence that Dr. Breuning had done some behavioral assessments at Coldwater, but there was no evidence that a systematic drug/placebo manipulation study, following a protocol, was ever carried out. The Panel could find no evidence for the existence of even casual followup data. Dr. Breuning's explanation for not identifying the nurse respondent because he would "get the person in trouble" was not credible; he could not tell the Panel how supplying such information would affect the person allegedly involved.

After examining all the evidence, the Panel found that the reports of the dyskinesia studies contained serious and calculated distortions. The Panel concluded that the studies described were not carried out.

Dyskinesia Assessment Instrument

Sprague, Kalachnik, Breuning, Davis, et al. (1984) described a rating scale for assessing tardive dyskinesia in the developmentally disabled, the Dyskinesia Identification System-Coldwater (DIS-Co) and presented normative data. The Panel confirmed that developmental work on the instrument was done at Coldwater by Dr. Breuning and others. The data reported in this article are from Cambridge State Hospital (Minnesota) and were collected under the supervision of the second author, Dr. Kalachnik. The Panel identified no issues relevant to Dr. Breuning's involvement in this study.

Administrative Review of Drug Treatment

Ferguson, Cullari, Davidson, and Breuning (1982) described a technique of staff review designed to reduce medication prescription in the patient population. Decreased frequency of inappropriate behaviors was the variable on which medication adjustments were made. Patient behavior was discussed at monthly meetings of teams, each involving six professional staff and at least one direct care staff.

Coldwater is specified as the site for this study. Three programs there are reported separately, each covering a different timespan. Baseline data were abstracted from patient files; it is unclear how long patient behavior was observed and charted. Drs. Ferguson and Cullari, who were on two of the programs and reported on them, told the Panel they still had their summary data. Dr. Ferguson made minutes of his treatment team available to the Panel. Neither had seen Dr. Breuning's data on the third program. Other staff at Coldwater believed he had made the observations. However, although it is possible that this study was carried out as reported, it was not possible to verify that raw data existed for that portion contributed by Dr. Breuning. Therefore, the Panel could not draw any conclusion regarding the validity of this study.

Psychopharmacologic Treatment Studies

Beginning in 1980, a series of publications by Dr. Breuning and others reported on studies of the effects of psychotropic drug treatment on the mentally retarded. In 1980, Breuning, O'Neill, and Ferguson reported a 28-week study of 18 adult, institutionalized mentally retarded persons who had been identified for drug discontinuance. The design was complex, involving randomly assigned conditions of drug, drug and response cost, placebo, and response cost alone. The article gave detailed descriptions of residents' living units, staff characteristics and training, and observations of target (disruptive and/or aggressive) behavior at 30-minute intervals 24 hours a day, and states that informed consent had been obtained.

Coauthor Ferguson told the Panel that the data for this article had been collected by Dr. Breuning at Oakdale and that he had seen only charts or graphs prepared by Dr. Breuning. Staff members and colleagues at Oakdale said he never conducted human subject research there, and there is nothing in the official records of the institution to identify Oakdale as the research site. No consent forms could be found.

Breuning and Davidson (1981) reported on the results of IQ test performance of medication (neuroleptics) manipulation. Twenty-four adult, institutionalized mentally retarded subjects were observed under conditions of drug, placebo, standard, and reinforced test techniques. The article stated that informed consents were obtained.

Coauthor Davidson told the Panel his role on this paper was looking at the literature and working on drafts. He said the data had come from Oakdale and insisted such a study would not have been carried out at Coldwater because of the center practice on placebo use. Dr. Breuning himself told the Panel that the study had been carried out at Oakdale and various sites in Illinois. Again, staff members and colleagues at Oakdale said Dr. Breuning did no human subject research there. Dr. Breuning told the Panel he had conducted research in the Chicago school system, but the subjects in this study were institutionalized adults. Consent forms for a study like this one could not be found at either Oakdale or Coldwater.

Breuning, Ferguson, Davidson, and Poling (1983) reported a study of the standard and reinforced performance of 40 mentally retarded adolescents under drug (thioridazine)-no drug conditions in a double-blind, placebo controlled protocol. Behavior observations were recorded at 30-minute intervals 24 hours a day.

As with other studies, coauthors saw no raw data for this study. Each told the Panel he thought it had been carried out at Oakdale. Dr. Breuning himself told the Panel it was carried out at many sites in Illinois which he could not recall and at Oakdale. Inquiries at Oakdale preclude its being the site. The size (a pre-study trial involved 142 subjects) and complexity of design preclude this study having been conducted at multiple sites, and Dr. Breuning's account of his research activity in the Chicago area was not found credible in view of the fact that he could identify neither the investigators to whose research he had attached himself nor the sites where that research was conducted.

The Panel concluded that none of the described studies of psychopharmacologic treatment had been carried out.

Effects of Therapeutic Manipulation on Task Performance

The Panel reviewed six studies reporting on the effect of medication manipulation on task performance. Wysocki, Fuqua, Davis, and Breuning (1981) reported on the effect of gradual withdrawal of thioridazine on a matching-to-sample task with four adult, mentally retarded institutionalized residents at Coldwater who had been identified as candidates for drug withdrawal. The article was based on the primary author's (Wysocki) doctoral dissertation. The data are presented in a straightforward manner. The Panel confirmed through its site visit to Coldwater and through interviews that this work was carried out as reported.

Davis, Poling, Wysocki, and Breuning (1981) reported on the gradual withdrawal of an antiepileptic (Phenytoin, or Dilantin) on a matching-to-sample task and workshop performance in three mentally retarded subjects. Dosage reduction and administration of an inactive placebo at the 0 mg. level are described and the article states that double-blind procedures were used throughout. This article was based on Ms. Davis' Master's thesis. The Panel confirmed through interviews with the second and third authors that the matching-to-sample tests were carried out. A site visit to the Evergreen School adjacent to Coldwater confirmed that staff there had recorded workshop performance (assembly of a Bendix bicycle brake), using a form, and that Dr. Breuning and Ms. Davis had access to school records; and Ms. Davis told the Panel that school records were copied. There is a discrepancy on drug manipulation, however. Coldwater officials maintained that drugs could not be manipulated for research purposes and that placebos were not used there. Dr. Breuning said that placebos were used. Ms. Davis told the Panel that medication was not manipulated and placebos not used in her study, thus directly contradicting a a statement in an article on which she was first author and identical statements in her thesis. The Panel concluded that while the test and workshop performance evaluations had been carried out, there are significant irregularities in the published report. (Ms. Davis' comments on this report are appended at L.)

Breuning (1982) and Breuning, Davis, Matson, and Ferguson (1982) reported large, systematic, and complex studies of the effect of a neuroleptic (thioridazine) on intellectual and workshop performance of institutionalized mentally retarded persons. Both studies describe elaborate drug manipulations and use of placebos. In both, workshop performance was assembly of the Bendix bicycle brake. The articles reported on 84 and 80 institutionalized subjects respectively and would have required 80 weeks for the former and over 57 for the latter.

Dr. Breuning told the Panel that these articles report data collected in the Chicago area and at Coldwater, but he could offer no explanation as to why the two-site data collection was not indicated. His coauthors on the multi-author article saw no raw data and were under different impressions as to the site. The Panel found it inconceivable that such studies could have been carried out without the knowledge of colleagues or supervisors at Coldwater. Aside from verifying Dr. Breuning's access to clinical and school records, including observations on the brake assembly, the Panel found no evidence that such research had been carried out there. Nor did the Panel find credible Dr. Breuning's assertion that such data were collected at unnamed schools through studies by unnamed investigators in the Chicago area. The Panel concluded that the two studies described were not carried out.

An unpublished paper, Breuning, Sisson, Fultz, Marshall, and Bregman, reported on the effects on matching-to-sample performance of neuroleptics with 12 mentally retarded children. The list of coauthors and citation of a grant awarded to the University of Pittsburgh indicates the research was carried out there, but the paper reports a neuroleptic study. Dr. Breuning, when asked, said it was carried out at Pittsburgh and Coldwater. Pharmacy and other records at Pittsburgh indicated the subjects as reported were not available there. While matching-to-sample tests were run there, those scheduling the tests, and listed as second and third authors, indicated that the subjects were not scheduled as described and said the data they collected did not indicate the effects reported in this paper. While Coldwater officials denied the use of placebos there, Dr. Breuning indicated they were used without authorization. While some data might have been collected, the Panel found no evidence that the study described was carried out.

Breuning and Poling in Matson and Barrett (Eds.) (1982) included a report of a pilot study of dosage effects for a stimulant (methylphenidate) on behavior and performance (fixed-ratio test) of six mentally retarded, hyperactive subjects, four prepubescent and two adolescent. The study is described as double-blind and placebo controlled. This pilot is similar in many respects to work originally reported by Dr. Breuning as having been carried out at Pittsburgh and later attributed by him to work in the Chicago area between 1974-1977. As indicated elsewhere, the Panel did not find credible Dr. Breuning's account of his research activities in Chicago. The Panel concluded that the pilot study described was not carried out.

Multi-State Survey of the Institutionalized Retarded

Davis, Cullari, and Breuning in Breuning and Poling (Eds.) (1982) reported a multi-State survey said to have been carried out during the time Dr. Breuning was at Coldwater. It is discussed separately here because of several unusual aspects.

The chapter states that the authors gathered 15,000 names of retarded persons placed in foster group homes in four States; 3,750 names were selected and a two-page questionnaire was completed on each of 3,496 subjects.

As described, this project would have required a large investment of time on the part of many people in the community. On questioning, Dr. Breuning was able to provide the name of only one person who was said to have participated in the project, and that person told Panel staff that he had no knowledge of the study.

Reducing the data and putting it into the computer would have been a huge, time-consuming task, and Dr. Breuning said he had done all of it. The questionnaire alone would have been 6,992 pages of information. It was impossible to determine the number of data items since Dr. Breuning did not provide the Panel with a copy of the questionnaire. The computer center Dr. Breuning said he used for the analysis of this data had no record of his using their equipment.

Neither the first author nor the other coauthor ever saw any primary data, nor did they have any idea how such a large study had been paid for. Both stated independently that they were involved in preparing only the introductory portions of the work and that Dr. Breuning had arranged for data collection and analysis and had done most of the writing.

These considerations brought the Panel to the conclusion that the study described in this chapter was not carried out.

Reviews

Several review chapters and articles by Dr. Breuning with coauthors were prepared or published in 1982, after he had moved to the University of Pittsburgh.

In 1982, Breuning and Poling contributed a chapter on pharmacotherapy to Matson and Barrett (Eds.), Psychopathology in the Mentally Retarded. It reviewed classes of medications and their uses in the treatment of the mentally retarded. The chapter cited many of Dr. Breuning's publications.

In that same year, Ferguson and Breuning published a chapter on antipsychotic and antianxiety drugs in Breuning and Poling (Eds.), Drugs and Mental Retardation. This chapter also used several of Dr. Breuning's previously published articles in support of his position that drugs should be replaced with behavioral therapies.

A 1982 issue of Clinical Psychology Review carried an article by Breuning, Davis, and Poling. The article raised many questions about drug use with the mentally retarded, arguing that behavioral techniques have been shown to be more effective in improving and controlling the behavior of the mentally retarded. The article depended for its support, in large part, on work reportedly done by Dr. Breuning.

Dr. Breuning co-edited a volume with Dr. J.L. Matson, published in January 1984, Assessing the Mentally Retarded, which included two review chapters written by Dr. Breuning and other University of Pittsburgh staff members. One of these, written with Barrett, provided a survey of IQ test theory and a review of the more frequently used IQ test instruments. No data were gathered for the chapter. Five of Dr. Breuning's publications were cited.

Another chapter in the same volume, written with Sisson, reviewed at some depth the ethical and legal implications of pharmacotherapy, focusing on interpretations of court orders involving drug treatments. The chapter referred to several of Dr. Breuning's publications for support.

All of these review publications relied heavily on Dr. Breuning's own work which the Panel concluded was not carried out as reported. The publications, therefore, must be regarded as scientifically unsound and seriously misleading.

Stimulant Drug Use with Mentally Retarded Children

After he moved to the University of Pittsburgh, Dr. Breuning applied for and received a research grant from NIMH to study the effects of stimulants (methylphenidate and dextroamphetamine) in 48 hyperactive, mild to moderately retarded children. He described his own role as being responsible for overall project administration and coordination, including project staff supervision, monitoring assessment and treatment phases of the project, overseeing data analysis, and preparing all resulting reports and manuscripts.

At the end of a year, he reported to NIMH that just over 65 percent of children required for the methylphenidate studies and approximately 35 percent of those for the dextroamphetamine studies had completed the protocol. He reported the results of three studies. His second progress report, submitted in his application for continued grant support, reported six completed studies and a seventh about 65 percent complete. Completed studies reported included Poling and Breuning, published in 1983, in which the effects of methylphenidate on fixed-ratio performance of 12 children, 6-14 years old, were examined. The study was described double-blind and involved placebo. Breuning, Ackles, and Poling reported on the effects of methylphenidate on fixed-ratio performance of 11 adolescent subjects. Studies 3, 4, and 5 reported on methylphenidate studies in 13 adolescents ages 14-18, 24 children ages 6-12, and 14 children with a mean age of 8.95 years, respectively. Studies 6 and 7 reported on effects of dextroamphetamine on matching-to-sample performance of 12 and 13 pre-school children respectively. In this report, 11 publications were listed as published, in press, or in preparation. Seven presentations were noted.

The Pittsburgh Ad Hoc Committee and the Panel confirmed that subjects for the reported studies were unavailable on the Merck Unit during Dr. Breuning's tenure. Fixed-ratio equipment, reported in five studies, was not operational there. Coauthors saw no raw data, only summary data and figures prepared by Dr. Breuning. Colleagues and coauthors were under varying impressions and given different information by Dr. Breuning about the site(s) of the studies. Some colleagues, listed as coinvestigators on the application(s) or coauthors on manuscripts, were not aware until later that their names had been so used.

When Dr. Breuning met with the Panel, he acknowledged that none of the subjects described in the progress reports was studied at Pittsburgh. Instead, he maintained that he had come across an ongoing study, or studies, in Chicago area schools and that the data reported were all obtained there sometime between 1974 and 1977. He could not recall the names of any of the schools or investigators. Administration of drugs, use of placebos, double-blind procedures, and obtaining of informed consents were, he said, all the responsibility of the unidentified investigator(s). A data book produced by Dr. Breuning on 15 subjects had no dates, and no identification of sites or subjects, and it did not meet ordinary standards for reporting research data.

Regarding his first progress report, Dr. Breuning told the Panel that he had been inexperienced and uninstructed, and was told by university administrators that the progress report was not important, "just submit something." This account did not agree either with the Panel's observation of administrative practices at Pittsburgh or with the report, which was a very detailed and polished effort.

In explanation of the second progress report, Dr. Breuning offered the Panel a substantially revised report which, he claimed, was the one that should have been submitted. He said that he had written the original one while under pressure from personal problems. When it had been questioned by a colleague, he had revised it and left it with his secretary to be typed and submitted. He then left town for several days and had no occasion to check until Dr. Sprague had raised questions about his work and he had discovered the error. As to his not having carried out the proposed research at Pittsburgh, Dr. Breuning said that he had not found it necessary to initiate drug treatment, and the patient population in the Merck Unit had changed.

The Panel found Dr. Breuning's account entirely lacking in credibility for the following reasons:

In an interview, Dr. Breuning's former secretary denied categorically that she had been asked to substitute progress reports or that she had typed the purported revision. She said that Dr. Breuning had never indicated to her that she had made such a serious mistake. A scrutiny of administrative records at Pittsburgh produced no evidence of the existence of the revision at the time the application was submitted. Administrative officials, in fact, offered evidence that the revision had to have been made on a copy of a document that had already been prepared for final submission.

Dr. Breuning's statement that an incidental study of stimulant drugs was ongoing in Chicago, carried out by unknown investigators, in unknown places, and with unidentifiable subjects was not credible.

Dr. Breuning was aware that funds awarded to him were not for the purpose of reporting data collected 10 years earlier. His account of why he had not carried out the studies as proposed at Pittsburgh, that there was little need to initiate drug treatment, does not agree with his submission of an application for 4 additional years of support to continue the same drug manipulation studies on 65 more subjects on the Merck Unit and of an application (later withdrawn and not further analyzed here) to initiate a prospective stimulant drug study with child patients on the Merck Unit.

The Panel concluded that Dr. Breuning's preparation of two grossly distorted, but polished and detailed, progress reports could only have been a deliberate and intentional effort to mislead and deceive the Federal funding agency.

Contractual Work at the University of Pittsburgh

Regarding a series of subcontracts under grant MH-32206 for work at the University of Pittsburgh, the Panel received information that while routine testing was carried out, the terms of the subcontracts appear not to have been met. The Panel believes that the payment of grant monies on the subcontracts raises issues of grant accountability that should be pursued administratively by NIMH.

VIII. Impact of Dr. Breuning's Reported Research on the Field

Any assessment of the impact of Dr. Breuning's reported research requires an evaluation of its scientific significance and its related effect on the everyday treatment of retarded individuals in institutional and community settings.

Dr. Breuning's reported empirical work centered on the effects of drugs on the behavior of the retarded, with special emphasis on what he described in his publications as the undesirable side-effects of those drugs. His findings had an impact on the field at a time when most clinical practice and administrative policy bearing on drug treatment were based primarily on anecdote and clinical impression. Because of the dearth of empirical data, Dr. Breuning's publications were perhaps used more widely than might otherwise have been the case and were therefore subject to less critical scrutiny. Dr. Breuning made a strong impression on the mental retardation field with a small number of publications in which he described well-designed studies that produced relatively robust and straightforward findings. In only a few years Dr. Breuning achieved major standing and became one of the frequently quoted workers in this field of investigation. His reputation was only slightly diminished by reports from other workers of their failure to replicate his findings.

Dr. Breuning also appears publicly, giving addresses in which he uses his publications to support his recommendations on social policy and treatment practices, primarily in regard to the retarded residing in institutions (an example is appended at C). There can be no question that States (e.g., Connecticut) have amended policies governing treatment practices in an effort to be consistent with what Dr. Breuning reports as scientific findings in his public addresses.

Thus, on the basis of his publications, Dr. Breuning has achieved the status of a major worker in the field of mental retardation. His reported work has had a significant impact on (a) the knowledge base of this field, and (b) social policies concerning the care and treatment of the mentally retarded. Questions about that work, therefore, have very serious implications for both.

IX. Conclusions

Conclusions regarding Dr. Breuning

It is the unanimous conclusion of the Panel that Stephen E. Breuning knowingly, willfully, and repeatedly engaged in misleading and deceptive practices in reporting results of research supported by or citing Public Health Service grants MH-32206 and MH-37449; that he did not carry out the described research; and that only a few of the experimental subjects described in publications and progress reports were ever studied; and that the complex designs and rigorous methodologies reported were not employed. Dr. Breuning also misrepresented, implicitly or explicitly, the locations at which research was supposedly conducted. The Panel did not find credible Dr. Breuning's shifting explanations as to where the various studies were carried out and his ultimate contention that many were conducted years before in the Chicago area.

The Panel unanimously concludes, on the basis of all the facts, that Dr. Stephen E. Breuning has engaged in serious scientific misconduct.

Conclusions regarding others

Ms. Vicky Davis worked with Dr. Breuning at two of the possible research sites. At Coldwater her salary and tuition costs were paid directly from grant MH-32206 and she received some salary at the University of Pittsburgh through a subcontract under the same grant. She was involved in collecting data and working with Dr. Breuning on a number of studies. Ms. Davis was first author on two studies, one of which the Panel found to involve significant irregularities and the second of which the Panel found not to have been carried out as described. The Panel concludes that Ms. Davis, as first author, did not behave in a scientifically responsible manner in that she either was, or should have been, aware of the improper reporting of data and methods.

The studies and reports reviewed involved a number of other coauthors. The Panel did not investigate all coauthors in depth. Interviews that the Panel did conduct with all major coauthors revealed a pattern in which Dr. Breuning induced others, who sometimes had little or no involvement, into coauthorship. A pattern also emerged in which it became apparent that major coauthors had not examined the primary source data, or raw data, for these studies. In other instances, names were added to manuscripts or grant applications without the individuals' knowledge. The Panel notes that several individuals took appropriate action, e.g., Dr. Patrick Ackles and Ms. Lori Sisson, in questioning and attempting to verify data and in asking that their names be removed from manuscripts that they found questionable. In its limited review of the activities of other coauthors, the Panel found no evidence of knowing participation in scientific misconduct.

The Panel commends Dr. Robert L. Sprague for bringing to the attention of NIMH his concerns about Dr. Breuning's work and his continued cooperation with NIMH and the Panel in investigating those concerns. However, the Panel questioned Dr. Sprague's judgment in uncritically including Dr. Breuning's publications, on which he was himself not a coauthor, in his grant progress reports. The Panel also expresses its concern at Dr. Sprague's failure to adequately oversee the subcontract, under grant MH-32206, with the University of Pittsburgh.

Conclusions regarding grantee institutions

The Panel recognizes the responsibility of educational institutions to provide an atmosphere of academic freedom. However, such institutions also have an obligation to ensure responsible science and to pursue diligently any allegation of scientific misconduct brought to their attention. The Panel found that neither the University of Illinois nor the University of Pittsburgh adequately fulfilled these obligations.

The University of Illinois failed to conduct a thorough investigation. The committee appointed to look into the matter based its findings on secondary evidence provided by a single source, Dr. Sprague. The committee's findings were that Dr. Sprague had behaved appropriately in reporting his suspicions of Dr. Breuning's research and that Dr. Breuning's work did not impact on Dr. Sprague's research. While the University of Illinois committee found that there was cause to believe that Dr. Breuning had engaged in scientific misconduct, they did not pursue this.

Under its procedures, the University of Pittsburgh appointed, successively, three committees to look into the allegations of Dr. Breuning's misconduct. These committees were charged only with reviewing Dr. Breuning's research thought to have been conducted at Coldwater despite an initial and repeated request from NIMH that the University review his federally-funded research at the University of Pittsburgh. Once Dr. Breuning had resigned from the University, the third committee's charge was further restricted to ascertaining whether there had been misuse of Federal funds.

After further prompting by NIMH, and after this Panel had begun its investigation, a fourth committee was appointed. This Ad Hoc Committee, under the leadership of the late Dr. Robert Miller, expanded its charge and conducted an exhaustive review of University records and of Dr. Breuning's reported work at the University under grant MH-37449. The Panel commends the members of the Miller Ad Hoc Committee for their responsible and comprehensive investigation. It is the opinion of the Panel that if the initial University of Pittsburgh investigating committees had been given a more comprehensive charge, significant time would have been saved.

X. Comments and Response of Panel

In accordance with Public Health Service policy, the Panel's report was sent in draft for comment to Dr. Stephen E. Breuning, Ms. Vicky Davis, Dr. Robert Sprague, and the Universities of Illinois and Pittsburgh; their comments were considered by the Panel in preparation of its final report. The Panel found no reason to change the substance of its report or its conclusions. The Panel does, however, have the following observations on the responses received.

Dr. Breuning provided extensive comments. Those that pertain to the substance or findings of the Panel's report are addressed below. Dr. Breuning asserted that the Panel intimidated witnesses and that he himself felt intimidated. The Panel notes that none of the witnesses identified by Dr. Breuning have communicated such fears either during or after their interviews. The Panel believes that most parties interviewed, while impressed by the seriousness of the investigation, gave careful and measured testimony. Throughout its proceedings, the Panel made every effort to conduct a fair review and to make no a priori assumptions about Dr. Breuning's conduct. It should also be noted that Dr. Breuning was represented by counsel at his interview with the Panel on November 22, 1985; that the interview was terminated by Dr. Breuning, not the Panel, and the Panel continued its sessions after his departure; and that after that interview Dr. Breuning was given multiple opportunities to provide additional information to the Panel.

Dr. Breuning claimed throughout his comments that the Panel held him to nonexistent research standards. The Panel expected merely that the contents of published reports represent precisely and fully what research was done, why it was done, where it was done, how it was done, and its results. The fact is that Dr. Breuning failed to provide evidence that much of the work described in detail in his publications and reports was done. Dr. Breuning's publications present detailed descriptions of work that on the basis of internal and external evidence cannot reasonably be assumed to have taken place as described.

Dr. Breuning protested that the Panel's standards for placebo and double-blind conditions were too stringent, requiring pharmacy control. Dr. Breuning described, as an example, medication being administered in crushed or liquid form in subjects' food, as well as through pills inserted into blank capsules. The practices were defended by Dr. Breuning as representing placebo-controlled/double-blind procedures. None of these procedures, however, were described in any of the publications. This kind of obfuscation constitutes precisely the problem Panel members repeatedly confronted in trying to determine what had actually occurred.

While the Panel found that placebos were used informally at the Coldwater Regional Center, it found no evidence that placebo-controlled/double-blind procedures were used there as part of systematic research. At Oakdale, use of placebo-controlled/double-blind procedures in research would have required the review and approval of the research committee. The committee's files had no record of such a research proposal by Dr. Breuning.

In his response, Dr. Breuning defended the absence of consent forms for the investigations described in his publications which stated that consent was obtained for subject participation. Dr. Breuning suggested that in some instances verbal consent was obtained and that this explains the absence of signed consent forms. He claimed that in other instances consent forms were unnecessary because observations were based on medication changes taking place in the course of treatment, rather than as part of a drug protocol.

Neither explanation provided justification for the absence of records of consent in the face of repeated written and verbal declarations that consent had been obtained. Regarding the University of Pittsburgh, Dr. Breuning commented that the Medical School Human Rights Committee told him that placebo use, if for clinical purposes, did not require consent. However, Dr. Breuning was the recipient of an NIMH research grant; it is, and was, the policy of the Department of Health and Human Services that any research involving Department funds and using human subjects must include provisions for informed consent. Documentation of the receipt of informed consent is part of the expected and legally required routine record-keeping process associated with all of the research activities under review by the Panel.

Dr. Breuning stated that the Panel had held him to standards of data retention that were unreasonable, that no guidelines exist for how long data should be held, and that it is only reasonable to discard information that might compromise confidentiality by identifying subjects. The issue of data retention begs the question as Dr. Breuning has provided no credible evidence that, with few exceptions, the described research was conducted.

Dr. Breuning commented that he had provided the Panel books of raw and summary data and that the Panel statement that the books contained no dates and subject identifiers was inappropriate because the Panel never asked him for an explanation of how to read the codes or interpret the dates.

The notebooks offered by Dr. Breuning as containing the raw data he said that he had gathered in Chicago area schools provide notations for months and days, but do not indicate years. There is no internal evidence by which the books can be identified as related to any of the studies Dr. Breuning described in his publication. When interviewed, Dr. Breuning was asked:

Question:	Do you have more identifying data on those subjects?
Answer:	Nothing.
Question:	What are some of the dates that you have?
Answer:	Well, I would have to go back and get a calendar, because all that is on here is the month and day.
Question:	Not the year?
Answer:	Not the year.

In his comments on the Panel's report, Dr. Breuning stated that the data from the Chicago area were gathered through access obtained by students in courses he taught at Trinity College who had brief practicums at various mental retardation sites in and around Chicago.

In his 1985 interview, Dr. Breuning said of the Chicago data collection:

> It was something that I sort of stumbled onto that I don't know who was doing it, somebody, I believe, completing an M.D., Ph.D., or some other degree at one of the area medical schools, and I had asked permission to have access to this data which was not being collected, and in turn I would make it available or leave it with the schools, and all I needed to know after the fact for partitioning out what was done at what point in time.

Here again, Dr. Breuning's vague, shifting, and unsupported descriptions of his acquisition of the data he attributed to the Chicago area failed to provide any convincing or verifiable evidence of their origins. The data books, themselves, contain no internal evidence that would relate them to any particular research site or project. In essence, they amount to an agglomeration of numbers that could not be directly linked by Dr. Breuning, or the Panel, to any specific research.

Dr. Breuning's publications and reports describe in detail complex research designs that could not have been carried out at the multiple sites he now claims were the sources of subjects. His publications do not in any way indicate they were based on 10-year old data collected at multiple sites. Thus, even if it were possible to verify the origin of the data presented, it would in no way alter the misrepresentation of the facts in Dr. Breuning's publications and reports.

Throughout his response Dr. Breuning refers to clinical observations, suggesting these observations provided a basis for his published reports. He complained that the Panel did not interview his clinical supervisors.

Contrary to Dr. Breuning's statement, clinical supervisors and associates were interviewed and clinical data examined with respect to their relevance to reported research. With respect to the Western Psychiatric Institute and Clinic, the Panel interviewed all personnel who could have had knowledge of research by Dr. Breuning. Dr. Breuning suggests that observations abstracted from clinical charts constitute the basis for his publications, rather than the controlled studies he described. But, as in the preceding section, even if this were the origin of his material, Dr. Breuning, himself, would be supporting the charge of misrepresentation. Many of his publications, and his grant applications and progress reports, were carefully crafted and polished documents describing precise research procedures structured to answer specific questions about the use of neuroleptic or stimulant drugs with the mentally retarded.

Panel members and staff made every reasonable effort to locate and interview those whom it could assume might have known of research being conducted in the facilities where Dr. Breuning was employed. Panel members contacted those individuals named by Dr. Breuning as able to corroborate his research activities. In his meeting with the Panel on November 22, 1985, Dr. Breuning was specifically asked for the names of people who could verify his work. He offered the name of Mr. Fred Morris as a person directly involved in research described in his publications, and the names of Dr. Paul Koutnik and Dr. John Regan as persons who were aware of research he had conducted. All three failed to corroborate Dr. Breuning's account. Dr. M. O'Neill, whom Dr. Breuning now names as someone who should have been contacted, did not reply to a letter written on behalf of the Panel.

Dr. Breuning protested that the Panel had distorted his representation of his relationship with Mr. Morris. In the chapter, "Drug Use in Community Foster-Group Homes," by Davis, Cullari, and Breuning, Mr. Fred Morris is mentioned as having trained "home operators and group home staff" in the use of medications with the community-placed mentally retarded. In the November 22, 1985, meeting with Dr. Breuning, Panel members asked for the names of any persons who had collaborated with Dr. Breuning in collecting the very large data set described in the publication and Dr. Breuning gave Mr. Morris' name. Mr. Morris was contacted by telephone on May 21, 1986. The context in which his name had been used both in the publication and in the transcript of the interview with Dr. Breuning were described to him. Mr. Morris said his only contact with Dr. Breuning had been to invite Dr. Breuning to speak at a seminar in observance of Mental Health Month in 1981 or 1982. Mr. Morris was Director of the Calhoun County Community Mental Health Program and at that meeting, Mr. Morris offered to visit adult foster homes in the community to discuss drug use with owners and staff. He recalled that perhaps four foster home managers had responded to his offer. He said he met with them, but talked about the use of psychotropic drugs with the mentally ill, not the mentally retarded. He recalled that very few developmentally disabled persons were among the residents of any of the homes in the community for which he was responsible. Mr. Morris denied that his efforts were in any way associated with the type of training described in the article. More importantly, he said he had no knowledge of research of the kind described in the publication, and denied having provided any information to help identify subjects in the community.

Dr. Breuning said that his thesis adviser, Dr. Paul Koutnik, could verify his contact with the school system in Chicago where he said he had obtained data, from sources he could no longer identify, which were included in the data sets he reported from other sites. However, during a telephone interview, Dr. Koutnik said he knew nothing of any research associated with Dr. Breuning's involvement with the schools, and that he had only arranged for Dr. Breuning to teach a biology course to satisfy requirements for a teaching certificate.

The only other person Dr. Breuning said would know of his research activities was Dr. John Regan, formerly a fellow student in the Ph.D. program at the Illinois Institute of Technology and later a colleague at the Oakdale Regional Center.

Dr. Regan said he had conducted experiments with goldfish with Dr. Breuning at Oakdale, but that he knew nothing of any research with human subjects done by Dr. Breuning.

Regarding his progress reports on grant MH-37449 to the University of Pittsburgh, Dr. Breuning essentially reiterated what he had said during his interview with the Panel on November 22, 1985. Neither Dr. Breuning's statements to the Panel nor his comments on its draft report provide a credible explanation for his motive in having written an initial progress report on grant MH-37449 which he now acknowledges to have been "misleading" and which, in fact, reports work which he did not do as described.

In discussing the submission of the second progress report on MH-37449 with the Panel during his November 22, 1985, interview, Dr. Breuning said that the revision he offered the Panel and claimed should have been submitted by the University was typed by his secretary after he had left town and that he had seen only the cover page. He said, "What I signed was the cover sheet. The cover sheet was signed prior to me leaving town and the complete package assembled . . . and I assumed the corrections were what was going to be attached to that." He was asked if he had signed a cover sheet without seeing the rest of the application, and he said, "Yeah, that is standard procedure there. I mean, at least it was how I was instructed to do that." In his comments on the draft report, Dr. Breuning says now that he "most likely did retype this section myself." He now claims he had asked for an assembled copy of the application in final form for his review prior to leaving town. Staff at WPIC confirm that he could have had a copy in final form, and while this would explain his access to a paginated copy on which to make changes, it does not correspond with the account he gave the Panel in his November 1985 interview.

The Panel did not find Dr. Breuning's explanation persuasive, nor did he provide new verifiable or substantive information. Therefore, the Panel maintains its previously stated conclusion that his revised version of the progress report was prepared only after questions about his publications had been raised.

Dr. Breuning commented that the Panel did not question his results. Since the Panel found that he did not carry out the studies he reported, it regards the reported results as unsupported.

In his comments Dr. Breuning states that he cited NIMH grant support on many of his publications only because he was instructed to do so by Dr. Sprague, and not because federal grant funds were used in support of the research described. In its report, the Panel discussed the relation of each research grant cited to

Dr. Breuning's work. Dr. Breuning's comments provide no basis for considering any of the studies discussed as outside of the Panel's purview.

Upon review of Dr. Breuning's response to the draft report, Panel members found that his comments were not persuasive. They were, in the main, a more strenuous repetition of what Dr. Breuning had said in his interview with the Panel. The Panel members maintained their conclusion that Dr. Breuning had engaged in a lengthy and premeditated course of scientific misconduct with the intent of misleading the scientific community and the federal granting agency.

Ms. Vicky Davis commented in regard to Davis, Poling, Wysocki, and Breuning (1981), that she either misunderstood the Panel's question regarding use of placebo, or the Panel misunderstood her answer. She stated that "there were no drug manipulations for research purposes and placebos were certainly used." The Panel notes this.

Dr. Sprague commented on the timetable of the investigation, dating events from his December 20, 1983, letter to NIMH. The Panel notes that its investigation began only with its first meeting on March 12, 1985. This was after the NIMH had awaited the results of the University reviews and had also spent a number of months obtaining background information to be used by the Panel.

Dr. Sprague commented that he noted great similarity between Appendix I of the draft report and material he sent to NIMH on January 9, 1985. Dr. Sprague sent material charting characteristics of subjects and research design. The appendix to the Panel's report included material garnered from interviews with 74 persons at 8 sites and the Panel's detailed analysis of each study, including its relation to other studies. The Panel notes that similarity is to be expected since both analyze aspects of the same studies.

Dr. Sprague expressed "amazement" that the Panel report did not mention

> . . . one of the most important facts in the investigation. The University of Pittsburgh obtained early in their investigation Dr. Breuning's actual confession of falsification. This fact is documented in the Adler, Michaels, and Lee letter of February 17, 1984 which states, 'Dr. Breuning admitted to us that statements in the abstract were false.'

The Panel notes that the statement refers to only one abstract, that the letter referred to is appended to the Panel report, and that the Panel interviewed Dr. Breuning directly regarding the abstract and addressed this issue specifically in Appendix I.

Dr. Sprague noted that the report did not mention an issue of possible plagiarism. The Panel looked into this matter and found no basis for proceeding further.

Finally, Dr. Sprague found problems with the balance of the report in that he was criticized for "failure to adequately oversee the subcontract" at the University of Pittsburgh and he noted that this involved oversight from 500 miles away and involved the operations of another university.

The Panel's observations, below, regarding University of Illinois' comments on this subject pertain here. The Panel further notes that Dr. Sprague initiated the subcontract and that he visited Pittsburgh during its course. Dr. Sprague told the Panel that he received no useful information from the subcontract. However, as late as September 29, 1983, Dr. Sprague wrote Dr. Breuning that he was recommending an increase in the subcontract for the next year. The date of this letter is after the date Dr. Sprague said his suspicions about Dr. Breuning's reports were significantly heightened (see Appendix A, letter from Dr. Sprague to Ms. Reatig). The Panel found no basis for amending its statement of concern.

In commenting on the limits of the University of Illinois' role and responsibility, the University stated that Dr. Sprague was the only person involved who was a University of Illinois faculty member, that no other University of Illinois faculty member had research interests closely related to the area of alleged scientific misconduct, and that none of the studies called into question were conducted on the campus of, or at sites related to, the University of Illinois.

The Panel report reviews 20 publications specifically citing grant MH-32206 awarded to the University of Illinois on which Dr. Sprague was principal investigator. Those publications were listed by Dr. Sprague in his annual reports of progress under his grant; Dr. Breuning's work at Coldwater was a formal part of Dr. Sprague's grant applications and reports; Ms. Vicky Davis, a project staff member at Coldwater, was paid directly by the University of Illinois from grant MH-32206; and the University of Illinois contracted under grant MH-32206, with the University of Pittsburgh, for further work by Dr. Breuning. The Panel continues to believe that the University of Illinois had a responsibility beyond notification to NIMH and review of the propriety of Dr. Sprague's conveyance of his concerns to NIMH.

The University of Illinois commented that in the absence of specific suggestions as to how Dr. Sprague might reasonably have more adequately overseen the subcontract at the University of Pittsburgh, it believed that there was not a basis for the Panel's expression of concern at Dr. Sprague's failure to adequately oversee the subcontract, under grant MH-32206, with the University of Pittsburgh. Since Dr. Sprague stated to the Panel that he received no useful information from Dr. Breuning under the subcontract, and since the subcontract was to include WPIC subjects in all aspects of grant MH-32206, the Panel's concern remains.

The University also commented that at no time after submission of its ad hoc committee report to NIMH did it receive notification that it had fallen short in any respect in its efforts to cooperate fully in the investigation. The Panel notes that on August 23, 1984, the Acting Director, NIMH, notified the University of Illinois that NIMH was undertaking its own investigation "because several issues remain unanswered by both the University of Illinois and the University of Pittsburgh reviews . . . ."

The Panel notes that the University of Pittsburgh had no comments.

XI. Recommendations

Specific Recommendations

In view of the Panel's conclusion that Dr. Stephen E. Breuning engaged in serious scientific misconduct, the Panel recommends:

- that Dr. Stephen E. Breuning be barred, for the maximum period of time permissible, from receiving PHS funds in support of research or related scientific, educational, consultative, or other activities. This provision is meant to apply to support either directly provided to Dr. Stephen E. Breuning or through his employment as staff on projects awarded to other individuals or institutions;

- that grant application MH-37449, for which an award was made to the University of Pittsburgh for Dr. Stephen E. Breuning's research, as well as progress reports and the report of this Panel, be referred to the Department of Justice with a recommendation that prosecution of Dr. Breuning be considered.

- that the Universities of Illinois and Pittsburgh, sponsors of grants under which Dr. Stephen E. Breuning received PHS support, be notified of the findings of the Panel and that relevant officials at other sites at which Dr. Breuning's research was alleged to have been carried out be so notified;
- that the present employer of Dr. Stephen E. Breuning be notified of the findings of this Panel;
- that all relevant professional associations and licensing or certifying bodies, and State agencies responsible for the care of the mentally retarded, be notified of the findings of this Panel;
- that all coauthors of publications with Dr. Stephen E. Breuning which were reviewed in this Report be notified of the findings of this Panel;
- that editors of relevant journals be notified of the findings of this Panel so that appropriate measures can be taken to advise readers, researchers, and others of these findings, and that journal editors be made aware of the capability of the National Library of Medicine to provide notice of retraction through MEDLINE and Index Medicus;
- that the findings of this Panel be made public to counteract the effect of unsubstantiated research reports;

General Recommendations

Responsibility for Publications and Presentations

During the course of this investigation, the Panel found instances in which some of the coauthors of Dr. Breuning's publications stated that they had little or no involvement in the work reported. They acknowledged that they had never seen raw data or the work in progress, nor had they been involved in generating the ideas for the studies. In some cases, their appearance as authors involved only an invitation from Dr. Breuning and editorial work in preparing the manuscript. In one instance, the first author indicated that she had almost no involvement in a large-scale study except helping to prepare the manuscript (Davis, Cullari, and Breuning; "Drug Use in Community Foster Group Homes"; see Appendix I, pp. 36-42). In other instances, individuals stated that they were listed as authors without their knowledge.

The Panel believes that as part of the process of communication between author and reader, the significance of authorship should be clear to both. In the view of the Panel, authorship should convey to the reader that each author has a measure of responsibility for the integrity of the published work.

The Panel recommends to editors of leading journals the consideration of the issue of what authorship implies, and that a statement of a journal's policy be provided to all authors of submitted manuscripts with a request for their signed agreement to the policy prior to publication. Although policy in regard to authorship may vary from journal to journal, a published statement of policy will enable both the author and the reader to make the same assumptions.

Panel members consider the standards of the International Committee of Medical Journal Editors published in The Lancet (September 14, 1985, p. 595) to be a promising basis for such policy.

Responsibility of Principal Investigators and Grantee Institutions

The Panel reiterates the importance of the principal investigator's responsibility for the scientific conduct of the research for which a Public Health Service grant is awarded, a responsibility specifically assumed when the principal investigator signs the grant application. This responsibility includes that for work not directly conducted by the principal investigator. The sponsoring institution also assumes responsibility for complying with Public Health Service terms and conditions of support as well as for the accuracy of grant application information.

The responsibilities of the principal investigator and the sponsoring institution should include, at a minimum, the assurance that research of the kind proposed can be carried out and that informed consents for human subjects are actually obtained.

The Panel recommends the development of model procedures and best practice guidelines, and their dissemination to research grantees.

Procedures for Future Investigations

This Panel spent nearly 2 years investigating one case of scientific misconduct. This effort was costly in time to Panel members and NIMH staff and required expenditure of significant amounts of Federal funds. The Panel members believe that procedures should be developed to avoid repetitions of this onerous process. In this case, although an investigation was undertaken by the University of Illinois and several were carried out by the University of Pittsburgh, none was definitive. The Panel, therefore, proposes that more explicit guidelines be developed so that more comprehensive and conclusive investigations will be undertaken at the institutional level.

To this end, the Panel recommends that implementation of Public Law 99-158, which requires that applicant organizations file assurances specifying development of policies and procedures for dealing with possible misconduct and agreement to inform the PHS of the initiation of an investigation of possible misconduct, include an investigative model. Such a model would require that a committee of inquiry be established at the institutional level. The committee should consist of the investigator's peers, a minimum number of members from outside of the institution, legal counsel, and an assigned coordinator from the funding agency. Rights of the investigator should be defined, as should procedures for conduct of the inquiry, preparation of reports, and recommendations. In cases in which extensive investigation may be necessary, a mechanism should be established for award of supplemental funds.

Establishment of more explicit guidelines for process at the institutional level could avoid expensive and prolonged investigations at the Agency level.

APPENDIX A
LETTER FROM DR. ROBERT L. SPRAGUE

1.

University of Illinois
at Urbana-Champaign

Institute for Child Behavior and Development

51 Gerty Drive
Champaign
Illinois 61820

Graduate College

December 20, 1983

Ms. Natalie Reatig
Pharmacologic and Somatic
Treatments Research Branch
National Institute of Mental Health
Room 10C-06 Parklawn Building
5600 Fishers Lane
Rockville, MD 20857

Dear Natalie:

It is with considerable regret and personal sorrow that it is necessary to write you a letter as Project Officer of my grant MH32206 about the possibility of misconduct of a colleague who has conducted studies with partial support of this grant. The letter is written in outline form to assist in conveying the processes and procedures I used to come to the above conclusion and provide information about the situation which is sometimes technical.

A. Chronology of events

1. On September 22 and 23, 1983, I visted Dr. Stephen E. Breuning (Department of Psychiatry, Western Pennsylvania Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine, 3811 O'Hara Street, Pittsburgh, PA 15261, telephone number 412-624-2331) as is my practice to visit routinely the sites where collaborative research is being conducted as part of my grant. Steve and Vicky Davis graciously invited me to visit their new home in a Pittsburgh suburb and to stay overnight with them. While discussing research the Thursday evening of September 22, I mentioned the difficulty we were experiencing in obtaining high interjudge reliability on the tardive dyskinesia (TD) ratings using the Dyskinesia Identification System - Coldwater (DIS-Co) at mental retardation facilities in Minnesotawhere my research is being conducted. Vicky responded that interjudge reliability was not a problem in her TD studies because she was obtaining 100% reliability with nurses as raters. Although I did not say much in reply, I was shocked and immediately alerted to the possibility of unsupportable data because I do not think it is possible for anyone, no matter how skilled a researcher, to obtain perfect agreement between two raters in an area as complex as judging abnormal movements associated with TD. The next day further doubts were aroused when Steve and I discussed his responder and non-responder data and the near perfect distinction in his various measures between these two categories of response to psychotropic drugs.

2. Steve kindly gave me a copy of his first Progress Report on his grant at the University of Pittsburgh entitled, "Stimulant Drugs with the Mentally Retarded" MH/HD 37449 (Appendix 1) which covered the period from July 1, 1982 to June 30, 1983 (although 1984 is listed on page 4 of the Report, the date seems to be a mistake). Because of the events mentioned in A.1. above, I read the report very carefully on the plane back home. More suspicions about his data were aroused, only one of which will be mentioned. If the report covers only one calendar year, then 261 working days (365 days minus 104 weekend days) are available not subtracting holidays.

Table 1

Facts on Studies, Number of Subjects, and Length of Studies Reported in MH/HD 37449 Progress Report

Study Number	Subjects	Sessions per Subject	Total Sessions	Length of Study in Days
1	12	4?	48	?
2	11	5?	55	?
3	13	7	91	49
4	24	7	168	49
5	14	9	126	63
6	12	9	108	63
7	13	7	91	49
Totals	99	48	687	273

Assuming that the 7 reported studies were conducted consecutively (it seems unlikely that two or more of the studies could not be conducted concurrently considering the limitations of the subject population and availability of experimental rooms), then it is difficult to understand how 273 study days (the total number of days it took to complete 5 studies not counting studies 1 and 2) could be completed in 261 working days. Moreover, these calculations do not take into account the ordinary circumstances of life that, at least, I am always plagued with in an experiment: subjects who miss appointments, research assistants who become sick and miss work, equipment breakdowns, etc.

3. As soon as possible after arriving home, I called together a few close colleagues who were familiar with Steve and his research. On September 26, 1983, these three people from the Institute for Child Behavior and Development met with me in my office to discuss problems with his data: Dr. Esther K. Sleator, a pediatrician who met Steve in 1979 when he first visited the Institute and who has read his papers; Ms. Rina K. Ullmann, a Research Associate who first introduced me to Steve and who was quite familiar with his reearch; and Mrs. Janis C. Rusch, a Research Assistant who had complained to me a number of months previously about Steve's papers and articles being "too good" and "too consistent" to be true. Since my suspicions were based on "soft information," we discussed what should be an appropriate course of action.

4. As a first step to clarify the situation, I began to look more closely at Steve's writings and closely inspect the reported results. During this time one of his grant applications to the March of Dimes with Dr. Patrick Ackles, a Post Doctoral Fellow at the University of Pittsburgh, was sent to me for review, and I declined to review it.

5. On November 7, 1983, Dr. Michael G. Aman (Department of Psychiatry, School of Medicine, University of Auckland, Private Bag, Auckland, New Zealand, telephone number 695-795-780) visited me, and the topic of Steve's research was mentioned in the context that Mike was obtaining different results with stimulant medication than Steve had reported. I indicated Steve's dose response data with stimulant medication using teacher rating scales showed a different pattern than I and other researchers had obtained. The next three days I

visited institutions in Minnesota at the request of the Court Monitor in the Welsch case and heard more disturbing comments about Steve's data and activities.

6. After meeting with Esther Sleator and Rina Ullmann again on November 14, 1983, it was decided to contact Dr. Ronald S. Lipman (Johns Hopkins Hospital, B6, Phipps Clinic, 600 North Wolfe Street, Baltimore, MD 21205, telephone 301-995-3065) for a number of reasons: he was a scholar familiar with the area; he was retired from the Psychopharmacology Research Branch of the National Institute of Mental Health (NIMH) and was quite knowledgeable about their procedures; since he was no longer in the employment of NIMH, the phone call could not be construed as an official complaint to the agency, and I was reluctant to make such an official complaint at that time due to the "softness" of the evidence; and he was independent of the situation and could, thus, give unbiased advice. I called him on November 15, 1983. He subsequently requested my permission to share confidentially the information with Dr. Mitchell Balter (Applied Therapeutics and Health Practices Program, National Institute of Mental Health, Room 9C-23 Parklawn Building, 5600 Fishers Lane, Rockville, MD 20852, telephone number 301-443-3946) for his advice and counsel, and I agreed on the basis that the information would be kept confidential and not perceived as an official complaint at that point.

B. ACNP abstract

1. On June 20, 1983 I invited Steve and four other people to participate in a proposed symposium to be presented at the annul meeting in December of the American College of Neuropsychopharmacology (ACNP); a copy of the letters are in Appendix 2. The proposal was accepted, although Dr. Garth Graham subsequently declined to speak.

2. Although I requested abstracts of their papers by October 10, 1983 (Appendix 3), Steve sent me a copy of his abstract (Appendix 4), which he mailed directly to ACNP sometime in November. Note carefully that his description of the follow-up study in the abstract states there were 45 subjects followed for 2 years with 6-month assessments.

3. I did not realize the possibility of a discrepancy between what was written in the abstract and what I knew was possible at Coldwater Regional Center, Coldwater, Michigan where the follow-up study was conducted until November 28, 1983 when I called Dr. C. Thomas Gualtieri (Department of Psychiatry, School of Medicine, University of North Carolina, Chapel Hill, NC 27514, telephone number 919-966-5161) about the first of three programs on tardive dyskinesia which CBS News broadcast on the evening news that day; both Tom and I had talked to CBS News extensively about the program. Tom mentioned that Steve would be presenting 2 years of follow-up TD data at ACNP, and I immediately realized there might be a problem when Tom made that comment.

4. The next day, November 29, 1983, I again carefully checked the abstract and numberous papers written by Steve. It became apparent that the follow-up study reported in the abstract was a continuation of the published study of Gualtieri, Breuning, Schroeder, and Quade. Tardive dyskinesia in mentally

retarded children, adolescents, and young adults: North Carolina and Michigan studies. *Psychopharmacology Bulletin,* 1982, *18,* No. 1, 62-65 (Appendix 5). The Gualtieri, Breuning *et al* paper clearly stated the subjects were from Coldwater Regional Center (see page 62 of Apendix 5). Since I had visited Coldwater Center about three times after Steve left there about January 1, 1981 for a position at the University of Pittsburgh, I was aware that it was highly unlikely that 45 subjects could be followed for 2 years after his departure. To check this further on November 29, 1983, I called Dr. Neal A. Davidson (Director of Psychological Services and Behavioral Treatment Program, Coldwater Regional Center for Developmental Disabilities, P. O. Box 148, Coldwater, MI 49036, telephone number 517-279-9551) who handled TD evaluations for Coldwater Center. He told me it would be "near a miracle" for the data to be collected without his knowledge and that he did not know who "they [the subjects] are or where they are." To be absolutely certain, I called him again the next day, November 30, 1983 to re-confirm his earlier statements.

5. I tried to call Steve to confront him with the discrepancy between the abstract statements and Neal's statements, but I could not reach him since he was out-of-town until Sunday, December 4, 1983 when I called him at home. My phone call and questions about the discrepancy surprised Steve, to say the very least. I indicated I would send him an express letter (Appendix 6) the next day, December 5, 1983, requesting supporting documentaion on the existence of the subjects and their evaluations.

6. A few minutes after 8:00 a.m. Monday, December 5, 1983, Steve called me; he seemed very upset. He indicated he had worked all night after my call and that he could not find all the supporting documentation which I requested. He further stated he could only find 25 subjects who were *evaluated once* at 96 weeks or 4 months following the 80-week study of Gualtieri, Breuning *et al.* I said my express letter would be on the way to him within hours. When he asked me about presenting the paper at ACNP on December 12, 1983, I said he should not.

7. Because problems with the follow-up study raised questions about the Gualtieri, Breuning *et al* paper and because Tom Gualtieri was a member of the ACNP symposium and planning to present further data collected in collaboration with Steve, I called Tom on November 30, 1983 to alert him confidentially to the potential problem and likely possibility that I would block the presentation of Steve's paper at ACNP on December 12, 1983.

8. On Thursday, December 8, 1983, I received Steve's express letter to me with part of the requested documentation (Appendix 7). Note that the subject identification code which translates the identification numbers to the subject names has not been located and that only 24 subjects were evaluated once at 96 weeks.

9. I was out-of-town part of December 9 and 10, 1983 and did not talk to Steve by phone on those days, although we talked by phone daily or twice a day since my December 4, 1983 phone call to his home. However, I reached him at home, Sunday, December 11, 1983. I indicated I received his December 7, 1983 letter (Appendix 7) but that my question as to why he reported in the abstract

45 subjects with 2-years of follow-up and then reduced it to 24 subjects with one 4-month evaluation was not answered. A number of questions about the supporting documentation was raised, only one of which will be mentioned. Steve stated he had personally examined all 24 of the subjects (see also Appendix 7). I asked him again if he examined all 24 of the subjects before he left Coldwater Center, and he said "yes." Then while flipping through the copies I asked him how he could have exmained subject 10-21 (I added the first number and dash to the ID number for my convenience) on January 5, 1981 when he had left for Pittsburgh before that date. He stated he probably did not leave until January 20, 1983. Again, another example of a discrepancy which is extremely disconcerting to me, and, for me at least, casts considerable doubt on the authenticity of the remaining 24 subjects.

10. My administrative superior, Dean Theodore L. Brown (Dean of the Graduate College and Vice Chancellor for Research, University of Illinois, 107 Coble Hall, 801 S. Wright St., Champaign, IL 61820, telephone number 217-333-0034) has been informed of the possible problems in Steve Breuning's research and that it has been partially supported by a Subcontract from the University of Illinois. Therefore, I am sending him a copy of this letter.

11. I did not permit Steve to present his paper at ACNP, although he requested to present a modified paper with 24 subjects.

C. Implications for other resarch

1. It is my understanding that Tom Gualtieri has requested supporting documentation for the data reported from Michigan in the Gualtieri, Breuning et al paper (Appendix 5) and that none of the raw data is available.

2. If raw data is missing for the Gualtieri, Breuning et al study, then it seems likely that data may be missing for Breuning, S. E. An applied dose-response curve of thioridazine with the mentally retarded: Aggressive, self-stimulatory, intellectual, and workshop behaviors - A preliminary report. Psychopharmacology Bulletin, 1982, 18 (1), 57-59 paper (Appendix 8) since it is very likely that there was considerable overlap between the subjects of the two studies. However, I have not, at this time, investigated this possibility.

3. The question, of course, then arises as to how much supporting documentation is available for Steve's series of studies.

D. Implications for MH 32206 renewal beginning April 1, 1984

1. It is my understanding that after calling Dr. Richard Marcus, Executive Secretary, on December 19, 1983 my renewal application has been recommended for funding with changes, the most important of which is the elimination of the request for a Subcontract to the University of Pittsburgh to support proposed research by Steve Breuning.

2. The question arises as to whether data collection procedures in my studies for the renewal and in my proposed studies has been tainted as described above, particularly in Section B. Let me state emphatically several points.

a. I do not condone nor will I tolerate imporper practices in scientific research. This should be partially evident from this letter which describes in some detail the development of my suspicions and how I investigated them. Although 16 other people from 4 other institutions have co-authored at least 39 papers, book chapters, or books with Steve since 1980, to the best of my knowledge, I am the first to report a set of suspicions and my evidence for them to the proper officials.

b. The research of Steve and my research has been, surprisingly, quite separate and distinct. Except for one paper primarily prepard by Tom Gualtieri, Steve and I have never published together (Gualtieri, C. T., Breuning, S. E., Sprague, R. L., & Campbell, M. A centralized data system for studies of tardive dyskinesia (Letter). Journal of the American Academy of Child Psychiatry, 1981, 21, 303-304). All of the research proposd in the renewal of MH 32206, except for the proposed University of Pittsburgh Subcontract which has been eliminated, will be done separately from Steve either at the University of Illinois or in mental retardation facilities in Minnesota.

Sincerely,

Bob

Robert L. Sprague, Ph.D.
Director

RLS/sb
Enclosures
cc: T. L. Brown, Vice Chancellor for Research, University of Illinois
J. Levine, Chief, Pharmacologic and Somatic Treatments Research Branch, National Institute of Mental Health

A. SPECIFIC AIMS

During the past 14 months we have conducted seven studies which we believe greatly advance what is known concerning the efficacy and behavioral effects of stimulant pharmacotherapy with hyperactive mentally retarded children and adolescents. (A complete discussion of our findings appear in Section C.) While our findings answer many questions, the findings have also generated many questions (see Significance section). The research proposed in this Competing Continuation application is designed to address these questions with the intent of providing clinicians with dosage recommendations for prescribing and evaluating stimulant medications as a part of the treatment provided to hyperactive mentally retarded individuals. Specifically, we plan to:

1. Evaluate the effectiveness of four dosages of dextroamphetamine in reducing the hyperactive behaviors of mentally retarded children between the ages of 6-12. This evaluation will include assessments of academic and laborator performance as well as social interactions (i.e., positive, neutral, and negative child/teacher and child/child interactions).

2. Directly compare the effectiveness of two dosages of dextroamphetamine and two dosages of methylphenidate with hyperactive mentally retarded children between the ages of 6-12. Again, there will be assessments of academic and laboratory performance as well as social interactions.

3. Evaluate the behavioral time-course of two dosages of dextroamphetamine and two dosages of methylphenidate with hyperactive mentally retarded children between the ages of 6-12.

B. SIGNIFICANCE

In 1937 Bradley (1) and Molitch and Eccles (2,3) published papers concernin the efficacy and behavioral effects of benzedrine. Since this time, methylphenidate and dextroamphetamine have become the medications of choice in treating attention deficits, aggressive/disruptive behaviors, impulsiveness, and restlessness in nonretarded children. It has been shown repeatedly that several stimulant medications, a) can dramatically improve the behavior of "hyperactive" nonretarded children, b) often enhance the effectiveness of other treatment modalities with these children, c) often improve the academic and cognitive performance of these children, and d) are relatively free of serious and/or permanent side effects.

Despite the clinical utility of stimulant medications in treating behavior commonly displayed by "hyperactive" nonretarded children, stimulant medications have not become widely used in treating similar behaviors being displayed by mentally retarded children. In 1970, Lipman (4) reported that less than 3% of the institutionalized mentally retarded individuals in the United States were receiving treatment with stimulant medication. Similarly, Cohen and Sprague (5) found the prevalence of stimulant use with institutionalized developmentally disabled individuals to be 2-3%. Most recently, Gadow (6) and Davis, Cullari, and Breuning (7) again found a 2-3% prevalence of stimulant medication use with the mentally retarded; however, all individuals sampled were residing in community settings (foster homes and group homes) rather than institutional settings. In each of these surveys methylphenidate was the most widely used stimulant medication followed by dextroamphetamine.

In view of the frequently reported excessive motor activity displayed by a large percentage of the mentally retarded, these prevalence figures are surprisingly low. For example, Rutter (8) used parent and teacher rating scales to assess behavioral problems in retarded children and found that three disorders and one symptom tended to recur more commonly among the developmentally disabled. These are the hyperkinetic syndrome, disintegrative psychosis, autism, and behavioral stereotypy (invariant repetitive movements). Similarly, Philips and Williams (9) studied 100 mentally retarded children referred to a child psychiatric clinic; 38 of the children were found to have psychotic symptoms and 49 had nonpsychotic behavior disorders. Subsequently, Philips and Williams (10) examined the incidence of hyperactivity in the aforementioned population. Children comprising the nonpsychotic group had an incidence of hyperactivity approaching 31% when diagnosed according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM II). On the other hand, the incidence of hyperactivity as diagnosed by DSM II criteria was 54% in the children presenting with psychotic symptoms. Thus, the incidence of hyperactivity in the mentally retarded is apparently much greater than one would assume from a 2-3% prevalence of stimulant medication use and much higher than in non-retarded school-age children in whom hyperactivity is usually estimated at less than 3%. While it cannot be assumed that hyperactivity is an inevitable outcome of mental retardation, the data suggest a strong association between mental retardation and the incidence of hyperactivity.

One reason for the limited use of stimulant medications with the mentally retarded is the lack of an adequate decision making data base in the stimulant medication/mental retardation literature. In the past decade there have been numerous reviews of this literature (11, 12, 13, 14, 15). The consensus has been that studies in this area are methodologically inadequate and/or incomplete investigations, yield drastically conflicting information, and rarely include comparisons across dosage levels. A brief review of this literature is warranted and is provided below. We will first discuss studies performed by others. This will be followed by a discussion of our work in this area.

Studies by Others

Methylphenidate. Of the studies examining methylphenidate with the mentally retarded there have been reports of improved classroom learning and behavior (16), enhanced achievement test and motor task performance (17, 18), and improved behavior as assessed via a rating scale (19). While the results of these studies support the efficacy of stimulant pharmacotherapy with the mentally retarded, methodologically equivalent reports have been contradictory. In one study it was found that the short-term memory performance of mentally retarded children was not affected by methylphenidate (20). Similarly, methylphenidate treatment yielded no significant changes in the frequency of stereotypic behaviors, non-stereotypic behaviors, rocking, and gross body movements (21, 22). Another study (23) found that methylphenidate was much less effective than a behavior management procedure in the modification of hyperactive classroom behaviors displayed by mentally retarded boys.

Most recently Varley and Turpin (24) and Aman and Singh (25) have conducted studies examining methylphenidate in the mentally retarded. Varley and Turpin examined two relatively low doses of methylphenidate with hyperactive mentally retarded children (IQs 49-77, ages 4-15). It was found that 50% of children responded favorably to the methylphenidate. Aman and Singh found little evidence of methylphenidate efficacy with mentally retarded adolescents and young adults (IQs 4-34, ages 13-26). However, these individuals were not selected because of hyperactivity but rather because of their primary severe autistic like behaviors. Also, only simple group analyses were performed with no attempt to separately analyze responders and nonresponders.

Dextroamphetamine. As with methylphenidate, the results of dextroamphetamine/mental retardation studies are inconclusive. One study found significant improvements in norm-referenced intelligence test performance (26), while another found significantly improved response latency and activity with several measures (27). However, there are also data showing no significant changes on measures of electromechanically and rating scale measured levels of activity (26, 28), or on stuttering (29).

Studies by Us

The seven studies conducted by us show several major conclusions and we believe do much to clarify the discrepant findings reported in the literature to date. Our major conclusions are:

1. Hyperactive mentally retarded children and adolescents show therapeutic and contratherapeutic responses to methylphenidate and dextroamphetamine similar to those evinced by hyperactive nonretarded children.

2. For therapeutic responders, at the optimal therapeutic dose (.05 mg/kg o methylphenidate with 90% of responders) maximal enhancement of learning and performance will most likely be obtained.

3. For therapeutic responders, at the highest dose of methylphenidate (1.0 mg/kg) stimulant induced perseverative responding (i.e., stimulus overselectivity) will likely occur.

4. For therapeutic nonresponders, there will most likely be a dose-dependent increase in hyperactivity and a reduction in learning and performance.

Our results coupled with the results of other studies suggest that methylphenidate will be very effective in reducing hyperactivity and enhancing performance with approximately 55-60% of mentally retarded children and adolescent who meet the following criteria:

1. Are above the age of six
2. Have an Abbreviated Conners' Teachers Rating Scale score above 15
3. Are not emitting severe autistic-like behaviors
4. Are mentally retarded due to no known etiology
5. Have no known neurological disorder

Further, our results suggest that dextroamphetamine will have similar therapeutic effects with about 30-33% of mentally retarded preschool children (3-6 years) who meet criteria 2-5.

The significance of these findings is readily apparent from the standpoint of stimulant drug use per se. However, the findings have greater significance in terms of overall drug practices with the mentally retarded. As we stated above, the use of stimulants with the mentally retarded is low. Neuroleptics, primarily thioridazine, are generally used to treat excessive activity, impulsivity, and other symptoms associated with hyperactivity when the client is mentally retarded. For example, we have found that mentally retarded individuals with a history of institutionalization typically were prescribed thioridazine while individuals with no such history typically received methylphenidate, even though the inappropriate behaviors being displayed by both sets of individuals were virtually identical. This may indicate that mentally retarded individuals with institutional histories are often being regarded as having "psychotic" problems while those with no history of institutionalization are regarded as having "hyperactive" problems. The reasons for this type of prescribing practice are unclear but may relate to the paucity of useful information currently available in the literature (7).

The use of thioridazine instead of a stimulant is problematic for several reasons. First, the efficacy for using neuroleptics with hyperactive mentally retarded individuals is not established (30). Second, neuroleptics are recommended as drugs of third choice with hyperactive non-retarded individuals (31). And third, the prescribing of neuroleptics versus other drugs (e.g., stimulants) in the treatment of hyperactive mentally retarded individuals is likely to result in impaired learning/performance and adaptive behavior with both therapeutic responders and nonresponders (30).

Thus, our findings to date have made great strides towards clarifying methodological reasons for contradictory findings in the literature. This in turn has allowed us to identify a group of mentally retarded clients who a) have a much greater likelihood of responding to a stimulant medication (primarily methylphenidate at this point) than the more frequently prescribed thioridazine (55-60% vs. 15-20% likelihood of therapeutic response); and b) will show enhanced adaptive behaviors rather than impaired adaptive behaviors.

In the proposed research we will build upon the research we have just completed in several ways. First, the dextroamphetamine dose-response curve study with 6-12 year olds will be useful for studying this drug along the same dimensions we have done so with methylphenidate (see Progress Report). Second, the direct comparison of dextroamphetamine and methylphenidate on a per client basis will provide information not addressed in the mental retardation literature. Third, the behavioral time-course data will allow for an understanding of how these drugs influence the clients during the 4-5 hour period following administration. And fourth, the addition of social interaction analyses will allow for another comparison of stimulant effects across mentally retarded and nonretarded children (see 32, 33 for studies by Whalen et al. and Pelham et al. of stimulant/social interaction effects with nonretarded children).

C. PROGRESS REPORT/PRELIMINARY STUDIES

1. Dates for the period covered by this progress report are 7/1/82 through 6/30/84. The report discusses our work completed to date as well as plans for the remainder of the project (e.g., studies to be completed, manuscript preparation deadlines).

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2. Fourteen staff are participating in this project. Their names, titles, dates of participation, and percentage of effort are:

	Name	Title	Dates of Services	% Effort
1.	Stephen E. Breuning, PhD	Assist. Prof.	7/1/82 - present	20%
2.	Rowland P. Barrett, PhD	Assist. Prof.	7/1/82 - present	5%
3.	Patrick K. Ackles, PhD	Post-Doc. Fel.	7/1/82 - present	10%
4.	Janice L. Forster, MD	Assist. Prof.	8/1/82 - present	5%
5.	Stewart Gabel, MD	Assist. Prof.	7/1/82 - 7/31/82	5%
6.	Edward J. Nuffield, MD	Assist. Prof.	7/1/82 - present	5%
7.	Lori A. Sisson, MA	Sr. Res. Assoc.	7/1/82 - present	100%
8.	Denise Frank, MEd	Res. Assoc.	9/1/82 - present	5%
9.	Sue Ann Fultz, MA	Res. Assoc.	7/1/82 - present	30%
10.	Vicky J. Davis, MA	Sr. Spec. Couns.	7/1/82 - present	10%
11.	Margaret C. Lunn, RN	Head Nurse	7/1/82 - present	5%
12.	Cynthia Campano, RN	Psych. Nurse	8/1/82 - present	5%
13.	Patricia Duffner, RN	Psych. Nurse	8/1/82 - present	5%
14.	Kathleen Phillips, RN	Psych. Nurse	8/1/82 - present	5%

3. Summary of Specific Aims

The original project was designed as an attempt to begin the systematic exploration of stimulant drug effects with mentally retarded individuals. There were three specific aims. These were:

1. Evaluate the effectiveness of three dosages of methylphenidate in reducing the hyperactive behaviors of mentally retarded children between the ages of 6-12.

2. Evaluate the effectiveness of three dosages of dextroamphetamine in reducing the hyperactive behaviors of mentally retarded children between the ages of 3-6.

3. Evaluate the effects of each dosage of both stimulant drugs on the academic and laboratory performance of hyperactive mentally retarded children.

Each of these aims has been met or is about to be met. A detailed review of the studies conducted to meet these aims is provided below.

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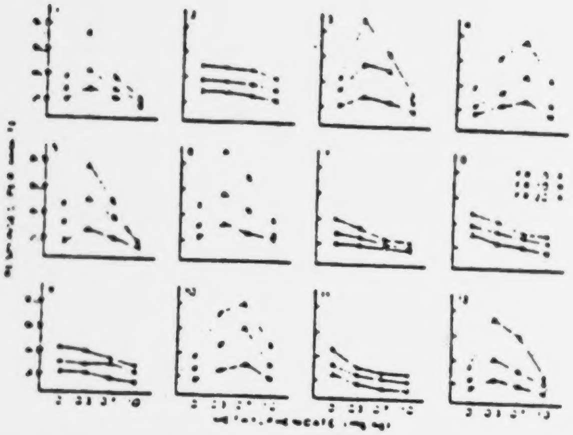
As stated earlier, this project began on 7/1/82. During the 14 months of the project we have completed six studies and are about 65% through a sevent study. One study has been published, one is in press, and manuscripts are being prepared for the other four completed studies. We are continuing with the seventh study.

STUDY 1. Poling A and Breuning SE. Effects of Methylphenidate on the Fixe Ratio Performance of Mentally Retarded Children. Pharmacology, Biochemistry anc Behavior, 18, 541-544, 1983.

The effects of methylphenidate on the lever pressing of 12 mentally retarde children maintained under fixed-ratio 5, 10, and 20 schedules of food reinforcement were examined. For five children, methylphenidate at oral doses of 0.3, 0. and 1.0 mg/kg produced generally dose-dependent decreases in respc rates, whereas for the other seve children the two lower doses increased response rates while the highest dose decreased respondin The differential effects of meth phenidate across participants co not be attributed to differences in control response rates or dem graphic factors. However, each c whose rate of fixed-ratio respon was increased by methylphenidate also demonstrated a therapeutic response to the drug. Figure 1 shows the performance data and a copy of this study appears in Appendix B.



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This study was the completic of our initial work in this area and was geared toward examining whether or not the dose ranges we selected should be further studied. The begin of this work was discussed in the original application but is included here beca it was completed as part of the grant proper. The main implications from this s are that mentally retarded individuals showing therapeutic responses to methylphenidate may also show increased rates of adaptive behavior. This stands in contrast to the results of recent studies showing dose-dependent decreases in adaptive behaviors of mentally retarded individuals receiving neuroleptic drugs regardless of whether there is a therapeutic response to the drug (1, 30) and ma be of clinical significance given that the rationale for using a neuroleptic versus methylphenidate with mentally retarded children appears to often be tenuo (7).

STUDY 2. Breuning SE, Ackles PK, and Poling A. Dose-Dependent Effects of Methylphenidate on the Fixed-Ratio Performance of Hyperactive Severely Mentally Retarded Adolescents. Applied Research in Mental Retardation, in press.

Dose-dependent effects of methylphenidate on the lever-pressing performance of 11 hyperactive severely retarded adolescents were examined during fixed-ratio

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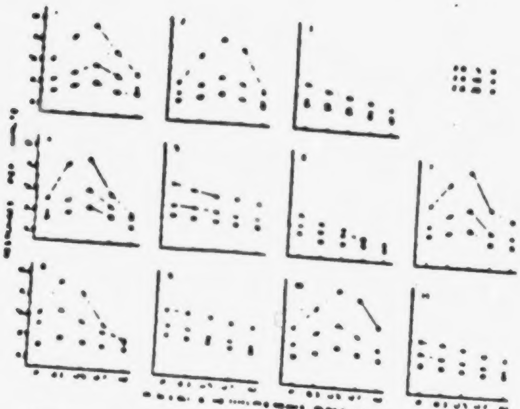
5, 10, and 20 schedules of food delivery. For five of the adolescents (45%), methylphenidate at oral doses of 0.3, 0.5, 0.7, and 1.0 mg/kg produced dose-dependent decreases in response rates. Six adolescents (55%) exhibited an inverted-U dose-response curve: five of these adolescents showed their fastest response rates at the 0.5 mg/kg dose with slower response rates at the lower and higher doses; one adolescent show the fastest response rate at the 0.3 mg/kg dose with slower rates during the placebo and higher dos conditions. Moreover, the slowes response rates for 10 out of the 11 adolescents occurred during th highest dose condition (1.0 mg/kg Spearman rank-order correlations between FR performance and abbrev Conner's Teacher Rating Scale scor indicated that FR performance duri the FR 10 and FR 20 conditions was highly correlated with degree of clinical response to methylphenidate. Figures 2 and 3 show the data and a copy of this study appears in Appendix B.



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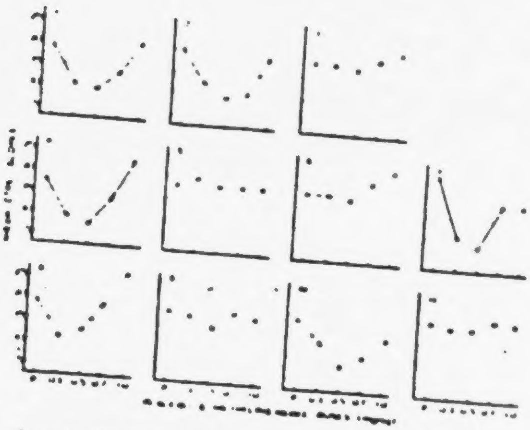

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The results showed that many hyperactive severely retarded adolescents will respond therapeutical to relatively low doses of methylphenidate. The findings also indic that hyperactive severely retarded individuals showing a therapeutic response to methylphenidate may als show increased rates of adaptive behavior. Presently, it appears as if the failure of others (25) to find a therapeutic effect of methylphenidate is likely due to their selection of mentally retarded individuals with severe autistic-like behaviors and/or their method of data analysis.

STUDY 3. Breuning SE, Sisson LA, Ackles PK, Nuffield EJ, Phillips KP, and Barrett RP. Multidimensional Dose-Response Curves of Methylphenidate with Hyperactive Mentally Retarded Adolescents. Manuscript in preparation.

This study was designed to examine the effects of methylphenidate (Ritalin) with hyperactive mentally retarded adolescents between the ages of 14-18 years. Thirteen children participated in the study, eight males and five females. The mean IQ of the group was 32.28 and the mean age was 16.3 years. Abbreviated Conners' Teachers Rating Scale (CTRS), time on-task, workshop, and lever pressing assessments were completed each day across conditions. Methylphenidate doses were 0.3, 0.7, and 1.0 mg/kg and dose administration was randomly determined for each child. The experiment proper consisted of seven conditions: placebo, dose 1, placebo, dose 2, placebo, dose 3, and placebo, respectively. Each phase lasted for seven days. Double-blind procedures were employed for medication and placebo conditions and existed for all staff and participants. The results indicated that therapeutic responders (N = 8) showed the reduced levels of hyperactivity (CTRS scores), increased time on-task, and enhanced performance on the lever pressing task. Optimal effects were generally at the 0.3 mg/kg dose. Non-responders (N = 5), however, showed relatively little change on all measures except for the highest dose where performance on all measures deteriorated. Figures 4, 5, and 6 show the data from this study. We are preparing this manuscript for publication.

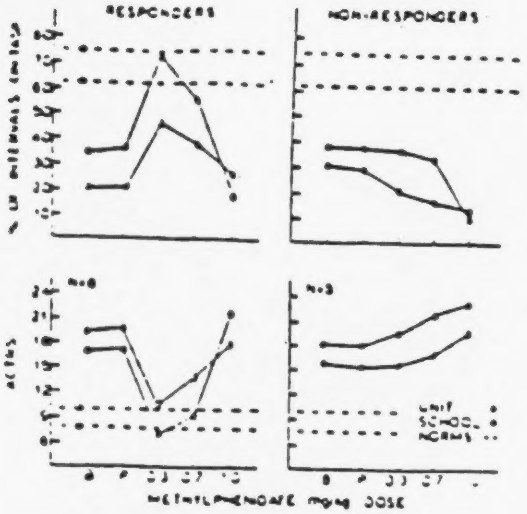

Figure 4. This figure shows the mean percentage of intervals on-task (top panels) and mean scores on the Abbreviated Conners Teachers Rating Scale (bottom panels) for 8 responders (left panels) and 5 non-responders (right panels) to methylphenidate across baseline (B), placebo (P), and three doses. Open circles depict data collected during unstructured (unit) activities while closed circles depict data collected during structured (school) activities. Similar data collected on non-medicated peers in both settings is represented as "norms".

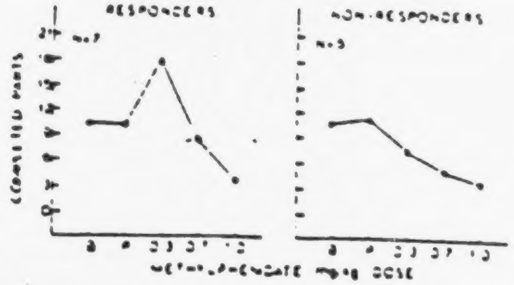

Figure 5. This figure shows the mean number of parts of a worksheet task completed per session by the 7 responders (left panel) and 5 non-responders (right panel) across the baseline (B), placebo (P), and three doses. There was incomplete data for one of the responders so this subject's data was excluded.

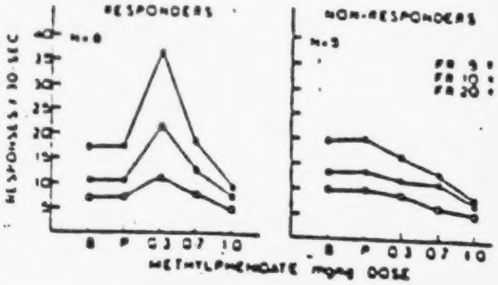

Figure 6. This figure shows the mean number of lever-press responses per 30-second period for the 8 responders (left panel) and 5 non-responders (right panel). Response rates are shown for each of the three reinforcement schedules (FR 5, FR 10, FR 20) across the baseline (B), placebo (P), and three methylphenidate doses.

The main findings of this study were that methylphenidate responders showed dramatic improvement along several clinical and laboratory dimensions. Non-responders showed dose-dependent worsening along these same dimensions. Also, this study supported the previous studies in suggesting that responders will typically perform poorly at a methylphenidate dose of 1.0 mg/kg.

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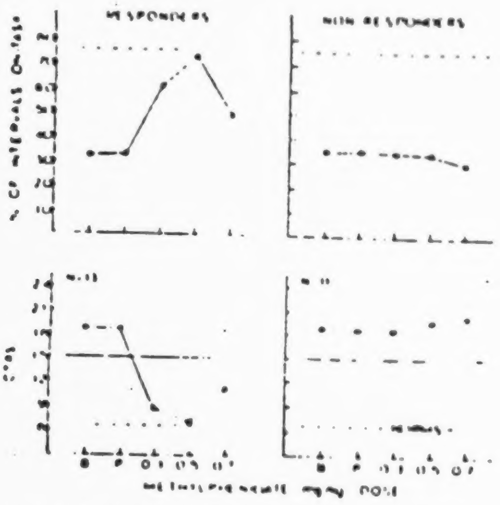
STUDY 4. Breuning SE, Sisson LA, Davis VJ, Ackles PK, Fultz SA, Duffner P, Forster JL, and Barrett RP. Multidimensional Dose-Response Curves of Methylphenidate with Hyperactive Mentally Retarded Children. Manuscript in preparati

This study was designed to examine the effects of methylphenidate (Ritalin with hyperactive mentally retarded children between the ages of 6-12. Twenty-f children participated in the study, 17 males and 7 females. The mean IQ of the group was 52.23 and the mean age was 9.7 years. Accuracy and speed of performa during a simple discrimination task served as the dependent variables. Also, Abbreviated Conners' Teachers Rating Scale (CTRS), and time on-task assessments were completed each day across conditions. Performance and accuracy were measu using a titrating delay matching-to-sample discrimination task. Methylphenidat doses were 0.3, 0.5, and 0.7 mg/kg and dose administration was randomly determi for each child. The experiment proper consisted of seven conditions: placebo, dose 1, placebo, dose 2, placebo, dose 3, and placebo, respectively. Each phas lasted for seven days. Double-blind procedures were employed for medication ar placebo conditions and existed for all staff and participants.



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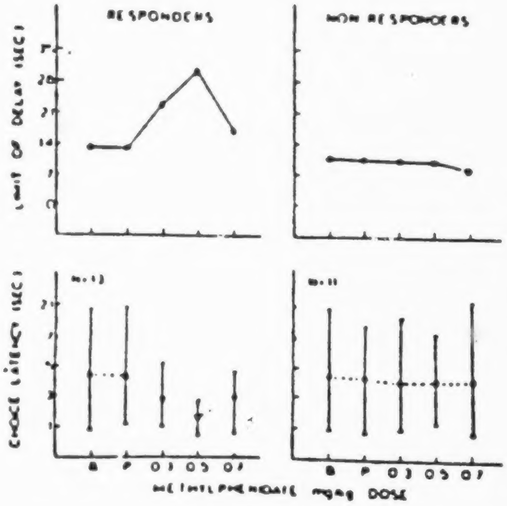

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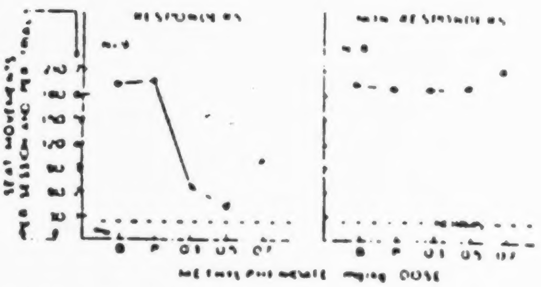

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The results indicated that therapeutic responders (N = 13) showed the reduced levels of hyper activity (CTRS scores), increased on-task, and enhanced performance the discrimination task. Optimal effects were generally at the 0.5 dose. Non-responders (N = 11), however, showed relatively little change on all measures except for the highest dose where performance on all measures deteriorated. Fig 7, 8, and 9 show the data from thi study. We are preparing this manuscript for publication.

STUDY 5. Davis VJ and Breuning SE. Effects of Methylphenidate on Titrating Delayed Matching-to-Sample Performance of Hyperactive Mentally Retarded Children. Manuscript in preparation.

The present study was designed to examine the effects of methylphenidate (Ritalin) with hyperactive mentally retarded children. Fourteen children were participants in the study, nine males and five females. The mean IQ of the group was 52.28 and the mean age was 8.95 years. Accuracy and speed of performance during a simple discrimination task served as the dependent variables. Also, Abbreviated Conners' Teacher's Rating Scales (CTRS) and time on-task assessments were completed each day across conditions. Performance and accurac were measured using a titrating delay matching-to-sample discrimination task. Methylphenidate doses were 0.3, 0.5, 0.7, and 1.0 mg/kg and dose administration was randomly determined for each child. The experiment proper consisted of nine conditions: placebo, dose 1, placebo, dose 2, placebo, dose 3, placebo, dose 4, and placebo, respectively. Each phase lasted for seven days. Double-blind procedures were employed for medication and placebo conditions and existed for all staff and participants. The results indicated that therapeutic responders showed the reduced levels of hyperactivity (CTRS scores), increased time on-task, and enhanced performance on the discrimination task. Optimal effects were generally at the 0.5 mg/kg dose. Non-responders, however, showed relatively little change on all measures except for the highest dose where performance on all measures deteriorated. Figures 10 and 11 show the data from this study. We are preparing this manuscript for publication.

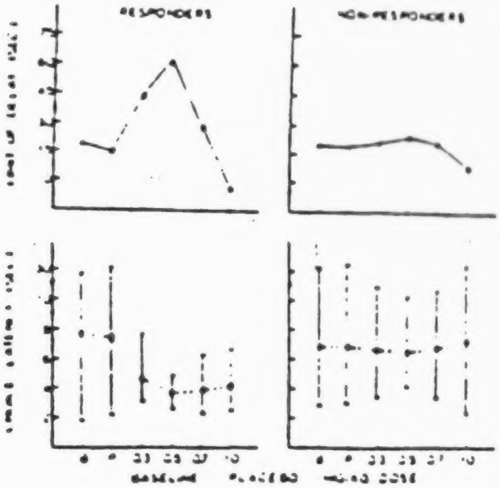

Figure 10. [illegible]

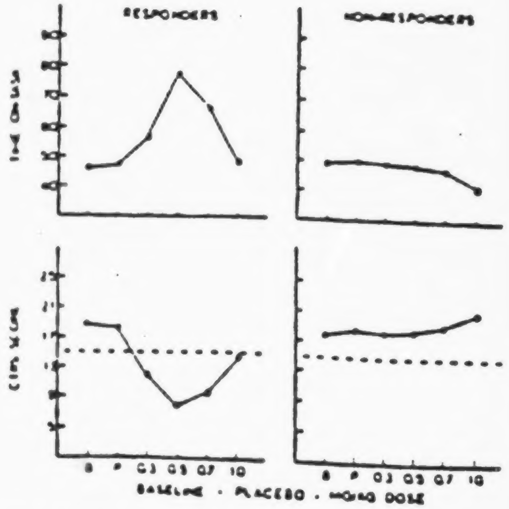

Figure 11. This figure shows the mean [illegible]

One of the most important findings in this study pertains to the latency data. It can be seen in Figure 10 that at the optimal dose there was a substantial decrease in response latency and variability as well as an increase in accuracy (i.e., delay). Also, at the higher doses response latency remains lower and less variable; however, accuracy is worse. This finding may replica

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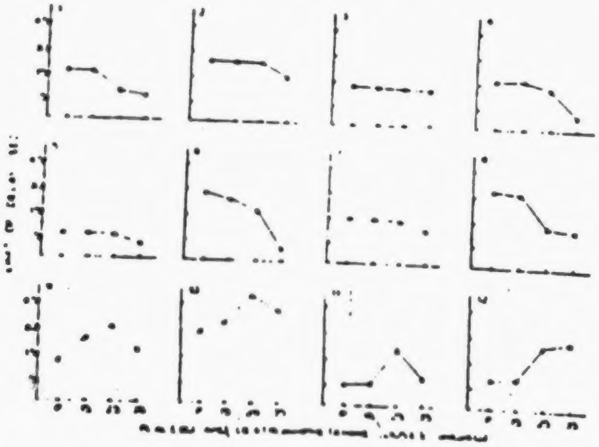
the stimulant induced "overselectivity" or "perseveration" reported by Sahaki and Robbins (34, 35) in the animal literature. The findings also suggest the need for studies to examine this issue with respect to attentional processes and learning in the mentally retarded.

STUDY 6. Ackles PK and Breuning SE. Effects of Dextroamphetamine on Titrating Delayed Matching-to-Sample Performance of Hyperactive Mentally Retar Preschool Children. Manuscript in preparation.

The present study was designed to examine the effects of dextroamphetamin (Dexadrine) with hyperactive mentally retarded preschool children. Twelve children were participants in the study, nine males and three females. The me IQ of the group was 56.48 and the mean age was 4.61 years. Accuracy and speed of performance during a simple discrimination task served as the dependent variables. Also, Abbreviated Conners' Teacher's Rating Scales (CTRS) and time on-task assessments were completed each day across conditions. Performance an accuracy were measured using a titrating delay matching-to-sample discriminati task. Methylphenidate doses were .15, .25, and .35 mg/kg and dose administrat was randomly determined for each child. The experiment proper consisted of ni conditions: placebo, dose 1, placebo, dose 2, placebo, dose 3, and placebo, respectively. Each phase lasted for seven days. Double-blind procedures were employed for medication and placebo conditions and existed for all staff and participants. Figures 12 and 13 show the data from this study. We are prepar this manuscript for publication



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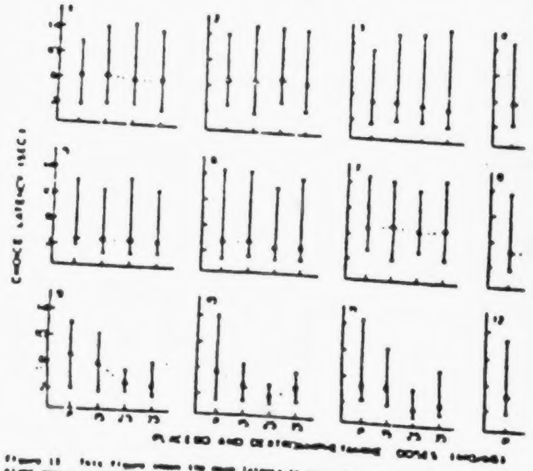

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The results of this study show the same responder/nonresponder dose-dependent effects found for methylphenidate. The noteable exception in this study is that a substantially smaller percentage of children responded to dextroamphetamine as compared to methylphenidate (i.e., 33% v. 55-60%). It is unclear whether this is a result of age (i.e., younger children), the drug, or an interaction.

STUDY 7. Breuning SE, Ackles PK, Sisson LA, Fultz SA, Campano C, Forster JL, Nuffield EJ, and Barrett RP. Multidimensional Dose-Response Curves of Dextroamphetamine with Hyperactive Mentally Retarded Preschool Children. Stu in progress.

This study was designed to examine the effects of dextroamphetamine (Dexedr with hyperactive mentally retarded preschool children. Thirteen children have so far participated in the study, nine males and four females. The mean IQ of the group was 53.28 and the mean age was 4.7 years. Accuracy and speed of performance during a simple discrimination task served as the dependent variables. Also, Abbreviated Conners' Teachers Rating Scale (CTRS), and time on-task assessments were completed each day across conditions. Performance and accuracy were measured using a titrating delay matching-to-sample discrimination task. Dextroamphetamine doses were .15, .25, and .35 mg/kg and dose administration was randor determined for each child. The experiment proper consisted of seven conditions: placebo, dose 1, placebo, dose 2, placebo, dose 3, and placebo, respectively. Each phase lasted for seven days. Double-blind procedures were employed for medication and placebo conditions and existed for all staff and participants. Figures 14 and 15 show the data for the 13 children. This study is in progress.

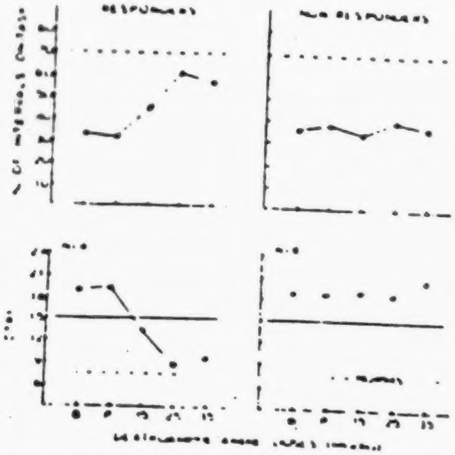

Figure 14. [illegible]

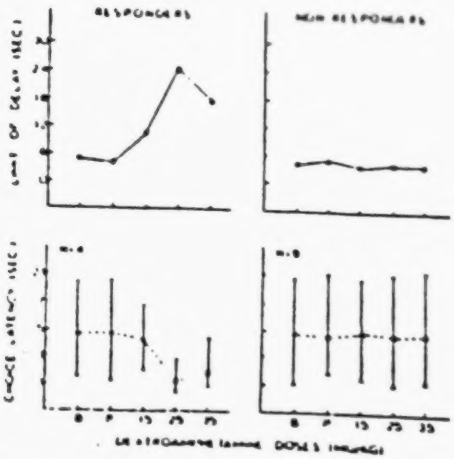

Figure 15. [illegible]

Thus far, the findings of this study are consistent with those of the methylphenidate studies with the exception of there again being many fewer responders.

4. Titles, complete references, publication deadlines, and major presentations.

1. Poling AD and Breuning SE. Effects of methylphenidate on the fixed-ratio performance of mentally retarded children. Pharmacology, Biochemistry, and Behavior, 18:541-544, 1983.

2. Breuning SE, Ackles PK and Poling AD: Dose-dependent effects of methylphenidate on the fixed-ratio performance of hyperactive severely retarde adolescents. Applied Research in Mental Retardation, in press.

3. Breuning SE, Sisson LA, Ackles PK, Nuffield EJ, Phillips KP and Barrett RP. Multidimensional dose-response curves of methylphenidate with hyperactiv mentally retarded adolescents. Manuscript in preparation - anticipated submission date is 11/1/83.

4. Breuning SE, Sisson LA, Davis VJ, Ackles PK, Fultz SA, Duffner P, Forster JL, and Barrett RP. Multidimensional dose-response curves of methylphenidat with hyperactive mentally retarded children. Manuscript in preparation anticipated submission date is 11/1/83.

5. Davis VJ and Breuning SE. Effects of methylphenidate on titrating delayed matching-to-sample performance of hyperactive mentally retarded children. Manuscript in preparation - anticipated submission date is 10/15/83.

6. Ackles PK and Breuning SE. Effects of dextroamphetamine on titrating delayed matching-to-sample performance of hyperactive mentally retarded preschoo children. Manuscript in preparation - anticipated submission date is 10/15/83.

7. Sisson LA and Breuning SE. Assessing medication effects. In JL Matson and SE Breuning (Eds) Assessing the Mentally Retarded. New York: Grune and Stratton, 1983.

8. Breuning SE and Gualtieri CT. Measuring dosages and dosage effects. In SE Breuning, AD Poling, and JL Matson (Eds) Applied Psychopharmacology: Methods of Assessing Medication Effects. New York: Grune and Stratton, in press.

9. Breuning SE and Sisson LA. Pharmacotherapy. In RP Barrett and SE Breuning (Eds) Treatment of Severe Behavior Disorders: Contemporary Approaches with the Mentally Retarded. New York: Plenum. Final manuscript due 10/15/83.

10. Breuning SE and Nuffield EJ: Mental Retardation. In M Hersen and SE Breunin (Eds) Pharmacological and Behavioral Treatment: An Integrative Approach New York: Wiley & Sons, Inc. Final manuscript due 11/1/83

11. Poling AD and Breuning SE. Medication effects: Neglected variables in applied behavior analysis. In M Hersen, RN Eisler and PM Miller (Eds) Progress in Behavior Modification. New York: Academic Press. Final manuscript due 1/1/84.

12. Breuning SE. Scientific Panel - Pediatric Psychopharmacology: New Issues anc Special Populations (Judith L. Rapoport - chair). Presented at the American Academy of Child Psychiatry Convention, Washington, DC, October, 1982.

13. Breuning SE. Keynote Address. Multidimensional effects of psychotropic drugs used with the mentally retarded: implications for mental health clinicians. Presented at the Minnesota Association for Behavior Analysis Convention, St. Cloud, MN, October 1982.

14. Breuning SE. Controversial aspects of pharmacotherapy with the mentally retarded. Presented at the Pennsylvania Chapter Meeting of the American Association on Mental Deficiency, Gettysburg, May, 1983.

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15. Davis VJ, McGonigle K and Breuning SE. Effects of ritalin on accuracy and speed of mentally retarded children's performance during a simple discrimination task. Presented at the Pennsylvania Chapter Meeting of the American Association on Mental Deficiency, Gettysburg, May, 1983.

16. Breuning SE and Poling AD. Some behavioral actions of pharmacotherapeutic agents in mentally retarded children and adults. Presented at the Behavioral Pharmacology Society Meeting, Philadelphia, May, 1983.

17. Breuning SE and Forster JL. Behavioral pharmacology with the mentally retarded: schedules of reinforcement, discrimination, and memory. Presented at the American Association on Mental Deficiency Convention, Dallas, May, 1983.

18. Breuning SE. Controversial treatment of severe behavior disorders: pharmac therapy with the mentally retarded. Presented at the American Associat on Mental Deficiency Convention, Dallas, May, 1983.

D. EXPERIMENTAL DESIGN AND METHODS

1. Overview of Research Strategy

The participants will be mentally retarded children between the ages of 6-12, having a DSM-III diagnosis of Attention Deficit Disorder - with Hyperactivity and an Abbreviated Conners' Teachers Rating Scale score of 15 or above. Two separate major studies will be conducted. In the first, four dosages of dextroamphetamine and placebo will be compared. The comparisons will be double-blind, placebo controlled, randomly counterbalanced, and assess changes in both targeted inappropriate behaviors and adaptive (laboratory, academic) behaviors as well as in child/teacher and child/child social interactions. In the second, two dosages of methylphenidate and two doses of dextroamphetamine will be compared using a counterbalanced design where each child receives each dose of each drug and a placebo condition. Again, the comparisons will be double-blind, placebo controlled, randomly counterbalanced, and assess changes in both targeted inappropriate behaviors and adaptive (academic, laboratory) behaviors as well as in child/teacher and child/child social interactions. Also, the behavioral time-course of each drug will be studied as part of this study. Repeated behavioral assessments at 30-45 minute intervals over a five-hour period following drug or placebo administration will occur. For each dosage (and placebo) time-course assessments will occur on the first and last day of a given condition.

2. Subjects, Setting, and Staffing

The subjects in this study will be mentally retarded children served by the John Merck Program for Multiply Disabled Children, Western Psychiatric Institute and Clinic. The JMP offers residential and day programming for children from 3 to 14 years of age who exhibit severely disordered behavior in addition to having a developmental disability. At any given time, the JMP treats 24 inpatients and 3 day patients. Approximately 120 children are seen by JMP each year. Records show that 15% of JMP children are receiving stimulant medication upon admission and that 20% receive a clinical trial of methylphenidate or dextroamphetamine as part of their therapeutic program. Approximately one-third of the children meet the diagnostic criteria of hyperactivity proposed for this investigation.

While all degrees and types of mental retardation are represented in the JMP population, the proposed study will only employ those children diagnosed as being within the mild or moderate ranges of mental retardation, as determined by American Association on Mental Deficiency criteria (36), and presenting no other neurological problems. In addition, children will be required to meet several medical criteria beyond satisfying the diagnostic requirements for mental retardation and hyperactivity. Specifically, a child will be excluded from participating if he/she:

1. is presently receiving any other form of medication (e.g., neuroleptic, anticonvulsant, etc.);
2. is presently on a restricted or special diet (e.g., Fiengold's diet);
3. has a developmental history significant for convulsive disorders (regardless of present status of control without medication); and/or
4. presents as mentally retarded due to a known etiology (e.g., Down's Syndrome, Sanfillipo Syndrome).

Comprehensive physical (including genetic and metabolic) and neurological examinations and blood/urine laboratory studies are routinely performed by a developmental pediatrician as standard practice within the medical admission protocol of the JMP. As needed, various specialty consultations (e.g., genetic, metabolic, neurologic, etc.) are readily available within the University of Pittsburgh's Health Center complex, which includes Children's Hospital of Pittsburgh among its six major hospital affiliates. The pediatrician is also a staff member of the Children's Hospital.

A total of 64 children will participate in the project. Thirty-two will be involved in the first study and 32 will be involved in the second study.

The JMP occupies the sixth floor at Western Psychiatric Institute and Clinic. Living space for the children and office space for the staff is provided. This study will require that observation of the children be made as they are engaged in their daily program activities, both in large living and play areas and in smaller classroom settings. In addition, two small treatment rooms will be used in the assessment of academic and laboratory performance. Each of these rooms will be furnished with a table and chairs and also materials necessary to carry out the assessment procedures. In addition, each room is equipped with a large plexiglass one-way observation window to facilitate unobtrusive observations of the children as they perform the required tasks and is completely equipped for unobtrusive visual and auditory recording. A full complement of professional and direct service staff is employed including six psychologists, three psychiatrists, four social workers, ten special therapists, five research associates, 20 nurses, 20 child care workers. In addition, the JMP serves as a rotation for a variable number of pre- and post-doctoral psychology students, psychiatry residents, and psychiatry clerks presently enrolled in either the Department of Psychology or School of Medicine at the University of Pittsburgh.

3. Experimental Design

a. Ongoing Medical, Educational and Behavioral Treatments. On admission to the JMP, all children are involved in comprehensive pediatric,

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psychiatric, intellectual, educational, and behavioral evaluations. Data from these evaluations are used to establish an overall treatment program for each child. Throughout the course of the proposed study, the procedures specified in each child's treatment program will be in effect. In general, educational programming follows a behavioral/developmental approach, with task difficulty increasing, and with new task requirements building on previously acquired skills. To facilitate on-task behaviors and to provide feedback regarding academic performance, behavioral treatment procedures are frequently employed.

The behavioral treatment procedures used in the JMP typically include positive reinforcement delivered contingent upon the occurrence of desirable behavior and time-out consequences for undesirable behaviors. Positive reinforcement may be simple verbal praise; however, in many cases, this verbal praise is accompanied by a piece of candy, cereal or other edible item, a preferred activity (e.g., playing with a favorite toy), or a token. Time-out consists of removing the disruptive child from an ongoing activity to a quiet place for a short period of time (e.g., 30-60 seconds).

The effects of these educational and behavioral treatments will be evaluated on an individual basis using the direct observation procedures described below and will serve as one dependent measure for both Study 1 and Study 2.

b. Dextroamphetamine Dose-Response Curve Study

1. Dosage Schedule. Four dosages of dextroamphetamine will be evaluated in this study. They are outlined in the Table below.

Drug	Group	N	Counterbalanced Sequence									
Dextroamphetamine	1	8	ND	P	.15	P	.25	P	.35	P	.45	P
	2	8	ND	P	.25	P	.35	P	.45	P	.15	P
	3	8	ND	P	.35	P	.45	P	.15	P	.25	P
	4	8	ND	P	.45	P	.15	P	.25	P	.35	P

ND= no drug (baseline), P = placebo. Each dose condition lasts 5 days. Each placebo condition lasts 2 days except for the first and last which will be seven days.

We expect no problems with the two day placebo period as numerous reports have shown that the half-life (pharmacological and behavioral) of dexedrine is about 6.5 hours ±2.5 hours following short-term (pharmacological and behavioral) use. Thus, in 48 hours we will easily achieve a washout of 4-5 half-lifes even in extreme cases (37, 38, 39, 40). Also, as shown by our completed studies, five days is sufficient to assess clinical response.

Each child will be evaluated under no drug (14-day Baseline), placebo, and four dosage conditions using a randomly counterbalanced design. Children in the methylphenidate phase and the dextroamphetamine phase will be randomly placed into one of the three experimental groups. These groups will differ in terms of the order of drug dosage levels given. This strategy will control for order effects.

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As stated earlier, the dosage levels to be employed in the dextroamphetamine dose-response study will be .15, .25, .35, and .45 mg/kg. In terms of mg/day measures, this represents dosage levels of approximately 2.7 mg/day, 4.5 mg/day, 6.3 mg/day, and 8.1 mg/day. These mg/day figures are based on two years of data showing that 6-12 year old children in our Program have a mean weight of 30 kg with a range of 25-50 kg and 3-6 year old children have a mean weight of 18 kg with a range of 15-30 kg.

Each child will be involved in this study for 49 days. At the end of this period each child will receive the most effective treatment, as determined on an individual basis.

Each child in the study will be given one daily dose of the stimulant medication, in the morning at approximately 8:00 a.m. (about 30 min prior to breakfast), during the course of the study. Dextroamphetamine will be administer elixer form (5.0 mg/5 cc). Placebos will be similar in taste and appearance and prepared by the WPIC Pharmacy. The medical staff of JMP (one pediatrician, three psychiatrists) will supervise drug administrations and also the daily medical review for adverse reactions.

2. Assessment of Hyperactivity. As stated earlier, children will be selected for participation in this study based on two criteria. First, the child must have received a DSM-III diagnosis of "Attention Deficit with Hyperactivity" from a child psychiatrist.

Second the child must have received a mean score of at least 15 on the CTRS. Masters-level Developmental Specialists will complete the CTRS for each of the children in their classrooms on a daily basis during the two weeks after a child is admitted to the JMP. The mean score of at least 15 will be derived across this two-week period (i.e., score of 15 or more on at least seven of the 10 days). From this data, appropriate candidates for the proposed study will be chosen. The use of the CTRS in this manner is a routine practice on our Program. Also, as suggested by Whalen et al. (41) the rating scale/questionnaire will be unobtrusivenely labeled (i.e., not as a "Conners'" scale).

In addition to initial screening of children for participation in the study, the CTRS will also be used in the evaluation of treatment effectiveness. A direct care worker (for unit behavior of the child) and a Developmental Specialist (for classroom behavior of the child) will complete the CTRS daily for each child in the study. This will be done at 12:00 noon each day in order to reflect the behaviors exhibited by the child during the period in which the stimulant medication is being assessed. Additionally, the questionnaire will also be completed by the direct care staff at 8:00 p.m. in order to assess behavior during the period of time when the medication would have dissipated from the child's system. We will also begin using the Iowa Conners Teacher Rating Scale (ICTRS). This is a 10-item, 4-choice scale reported to be useful in assessing hyperactivity and aggression as separate dimensions (42). It will be completed along with the CTRS.

3. Direct observation. Ongoing behavioral observations will provide information regarding the presence of a number of behaviors commonly associated with hyperactivity in mentally retarded children. Undergraduate psychology majors will be trained to serve as observers. Their training will be extensive, involving instructions in the use of the observation system and in the identification of target behaviors, numerous in vivo practice sessions, and a minimum

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of 12 test sessions. Practice and test sessions will be conducted in the regular JMP classroom setting, rather than in the special academic setting designed for this study. Test sessions will involve concurrent observation by the system trainer in order to assess reliability of observations (this procedure is described below). Observers will achieve a percent agreement score of at least 85% during 12 test sessions prior to serving in this study.

The observers will unobtrusively watch the children from an observation booth situated behind a one-way observation window in the treatment room. Continuous, 10-second, interval recording techniques will be used for data collection. Data collection will be facilitated by a tape which has been prepared to provide cues at 10-second intervals. At the end of each 10-second period, the occurrence of any or all of the following behaviors will be noted on a coded data sheet: self-stimulation; self-injurious behavior; aggression; and other disruptive behavior. Each of these behaviors will be operationally defined and specific examples of these behaviors commonly exhibited by each subject will be listed. Whether or not the child was on-task (i.e., manipulating the academic or play materials in the absence of any other appropriate behavior) during at least 60% of the observed interval will also be noted. Percentage of intervals in which appropriate (on task) and inappropriate (e.g., disruptive) behaviors occurred will provide dependent measures to be analyzed as outlined below. A scoring system similar to this has been used effectively by Whalen and colleagues (e.g., 41) with nonretarded hyperactive children.

Our direct observation system has been expanded so that we now also can score positive, neutral, and negative child/teacher and child/child social interactions.

Routinely, one observer will observe one child. However, reliability of observations will be assessed by having a second observer record the same behaviors at the same time during one-third of the observation periods. A measure of this reliability will be calculated using the standard percent agreement forumula: agreements/agreements plus disagreements x 100, where agreement is defined as both observers noting the occurrence of the same behavior during the same observation interval. In addition, reliability will be assessed statistically using Cohen's Kappa.

4. Assessment of Laboratory Performance. For each child, one 15-minute session will be scheduled daily, 5 days per week, during which he/she will be involved in laboratory assessment procedures. These will be scheduled to begin from 90 to 120 minutes after drug administration. Four children can be assessed each day with the equipment we currently have. The laboratory assessments will be performed using a matching-to-sample procedure.

4Ss/day

In a typical delayed matching-to-sample (MTS) procedure a sample stimulus is presented to the child. The sample then disappears and after a specified delay elapses, two or more comparison stimuli are then presented. The child's task is to choose the comparison stimulus which is identical to the previously presented sample stimulus. In titrating delayed matching to sample, the delay interval on a given trial is dependent upon the child's previous performance. Accurate performance by the child results in increasing the delay for the next trials. Using this procedure, Scheckel (43) determined the limit of delay reached by monkeys under a variety of drug conditions. With chlorpromazine, he found that the limit of delay decreased linearly with increasing dosages of the drug. Three recent studies involving the Principal Investigator have used MTS procedures with mentally retarded individuals and demonstrate the utility of MTS in psychopharmacological investigations. These studies are provided in Appendix C.

The MTS procedure to be used in the present study is described in detail in the reports appearing in Appendix C. Briefly summarized, the discriminative stimuli will be red, green and blue colors. At the beginning of each trial, a center response window is illuminated with one of the three colors. Once the child presses this center window, its illumination will disappear and two side windows will illuminate--one the same color, the other a different color. The position of these comparison stimuli will be varied randomly. Upon pressing the comparison stimulus which matches the initial sample stimulus, a tone and either a token or a piece of candy will be presented. Pressing the comparison which does not match the sample will result in a 10-second time-out. The data obtained during each trial will include the percentage of correct responses per session, number of trials per minute and latency to emit a choice response. A variation of this procedure which we will use is a titrating delayed matching-to-sample procedure which may be used to add an additional response measure analogous to many short-term memory or attending skill tasks. This procedure is as described above except that the time between the child's pressing the center window and illumination of the comparison stimuli will be increased in a systematic progression. Also, the seat in which the child sits during these sessions will automatically record seat movements per trial.

c. Comparison of Dextroamphetamine and Methylphenidate and Behavioral Time-Course Study

1. Dosage Schedule. Two dosages of dextroamphetamine and methylphenidate will be compared. A counterbalanced design will again be used. The 32 children will be assigned to one of four counterbalanced groups as described above. The design will parallel that described for Study 1 with the exception that two of the dosages will be dextroamphetamine and two will be methylphenidate. The counterbalancing, length of conditions, and method of dosage scheduling will be as we have stated above. The only exception will be that the methylphenidate and its placebo will be in tablet form.

At present we know only one of the dosages we will compare. This is 0.5 mg/kg methylphenidate. We are using this dosage because 90% of the responder in our previous studies responded optimally at this dosage. The remaining 10% were equally split at either the 0.3 or 0.7 mg/kg dosage. Although, the 0.5 dose was nearly as effective in each case. Once the dextroamphetamine study is completed, we will know what dosage of this drug is most likely to be optimal. Based on our initial work we believe it will be .25 or .35 mg/kg. At the completion of Study 1 we will also be in a better position to select the second dosages for the comparison.

Ideally, it would be best to directly compare at least three dosages of each drug. Due to practical considerations such as the necessary timeframe and our concern for unnecessary experimentation with the children, we chose the present design which should allow us to assess (compare) responding at optimal or near optimal dosages for virtually all children.

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2. Behavioral Time-Course. One issue of great interest to us is the length of time the drug's effects on laboratory task lasts following administration of the drug. Two studies (39, 40) have performed such assessments with nonretarded children. The authors of these studies believe such procedure to be useful as a means of classifying patients as potential thera responders in a single day. Our intent is to examine for similar utility with mentally retarded children.

The task we have chosen for this study is a fixed-ratio 20 lever pressing task (FR-20). As demonstrated in our first two studies reported in the progress report, the FR-20 schedule is a) very sensitive to stimulant dosage changes, b) can be performed by virtually any mentally retarded indiv and c) can yield much data in a ten-minute session. The task is quite simpl and merely involves the pressing of a lever. Each 20th press is reinforced with a piece of candy. A more complete description of the procedure is provided in our reprints in Appendix B.

[illegible] time-course data will be collected 12 times--twice durir the initial and last placebo phases (each is seven days) and twice during ea dosage condition (each is five days). Data will be collected on the first and last day of each of these conditions. The FR-20 task will be used with each session lasting 10 minutes. The sessions will be held just prior to dr [illegible] administration and 45, 90, 120, 165, 210, 255, and 300 minutes following drug or placebo administration.

We have elected to perform such assessments at the beginning and er [illegible] dosage condition to determine if the behavioral time-course varies as a function of continued treatment with the medication.

We have found that the children we serve easily tolerate this FR-2(task under such repetitive testing (i.e., no evidence of decreased enthusia: fatigue, etc.). And again, staff will be blind to conditions.

ssessment of Hyperactivity. This will follow the procedure [illegible] the dextroamphetamine dose-response study

irect Observation. This will follow the procedure described etamine dose-response study.

Assessment of Laboratory Performance. This will follow the pr([illegible] the dextroamphetamine dose-response study. The only exceptior [illegible] S assessments will be performed three days per week rather th. [illegible] because the fixed-ratio assessments will be conducted on the [illegible] days of the dosage condition (i.e., days 1 and 5).

Analyses

we have done previously, both group and individual analyses wil [illegible]. For research reporting the group analyses are generally emph. (but essarily) while we use the individual analyses for clinical pur;

up data analyses. The data from both studies will be analyzed [illegible] ple (split-plot) Latin Square Design (44). This design will all(

for separate dosage X children comparisons and an analysis of effects due to order of dosage presentation. Separate latin square analyses will be performed for each of the dependent measures within both studies.

Additionally, because it may be argued that baseline performance is a covariant, it will be necessary to test for equality of variance-covariance matrices. The procedure we will employ is that suggested by Box (45). Specifically, this test will allow us to determine that the variance-covariance matrix meets required conditions of symmetry.

For comparisons where significant interaction effects are obtained, we will proceed with tests of simple main effects. These tests will allow us to pinpoint whether effects occurred as a function of time. To determine specific group differences, post hoc comparisons using Duncan's New Multiple-Range Test will be performed on a pair-wise comparison basis.

Individual data analyses. Time series analyses will be conducted for each of the dependent measures within both studies. This will allow for the intensive analyses of a given child's individual responses to placebo-drug manipulations across the entire research protocol and will serve as a valuable adjunct to the traditional group statistics described above. The use of intrasubject analyses for each child's data is especially important prior to the making of treatment recommendations based on findings of the current investigation. These analyses will allow us to avoid the ethical problem of recommending treatment on the basis of group findings when, in fact, individual responses within a group may differ drastically.

5. Timetable

Beginning 7/1/84, children will be entered into the research protocol as they are identified as candidates in accordance with the diagnostic criteria to be used (i.e., DSM-III diagnosis; two standard deviations above the mean score for nonmentally retarded hyperactive children on the CTRS). A staggered entry by children into the research protocol for both drugs will decrease peak periods of assessments and also decrease the likelihood that observed effects of the selected drug are due to extraneous variables. For both studies assessments will be conducted daily across each experimental condition and include all dependent measures. Follow-up data will be collected at three and six month intervals following conclusion of active treatment. The table below outlines the specific timetable.

Months	
0-4	Project organization, training of staff on data collection procedures, development of materials necessary for studies.
5-23	Identification and assessment of children for Study 1.
24-42	Identification and assessment of children for Study 2.
43-43	Conduct data analyses, follow-up assessments, and prepare manuscripts for publication.

E. HUMAN SUBJECT'S PROTECTION

1. Consent Procedure

The objectives, procedures, and a clear statement of risks and benefit will be explained to the children (within the limits of their understanding) and their parents/guardians. Consent from the parents/guardians will be obtained in the presence of a witness prior to beginning the study. Consent forms as reviewed and approved by the University of Pittsburgh Medical School's Human Use Committee will be used. Once approved, copies of these forms will be forwarded to the appropriate study sections.

All information pertaining to children will be identified by code. Only these codes will appear on any data or documents used for evaluation or data analysis. No verbal or written information concerning a child will be released without express written consent. Publication of results will not include information which might result in a child's identification.

2. Potential Risks

There is a long history of the use of psychostimulant medication such as methylphenidate and dextroamphetamine in children. In general, these drugs employed within the dosage limits to be used in this study, have been relative free of side effects. Although good studies about both the benefits and possit risks in mentally retarded children while using stimulant medications are lacking (and is the reason for the present investigation), it is unlikely that serious physical side effects will occur. This seems especially true in view of the short duration of treatment for the various groups of children. The study's design makes it likely that possible deleterious effects in areas such as learning, attention, and behavior as a result of psychostimulant drugs in the retarded will be appreciated through the careful monitoring procedures described above.

The commonly known side effects of a physical or psychological nature while using stimulant drugs will, of course, be watched for carefully. Among the most common of these are: insomnia, decreased appetite, drowsiness, increased activity, and irritability. These effects are not infrequent when stimulant medication is first administered to children and if sufficiently severe will result in the child being withdrawn from the study (although these non protocol children may still have changes in their dosages with resultant benefits to them from the medication.)

Other less common effects of stimulant medication include: nausea, dizziness, headache, palpitations, blood pressure and pulse changes, cardiac arrhythmias, and abdominal pain. Having medical supervision in this clinical research center will hopefully alleviate problems of these types--most of whic are completely reversible on discontinuance of the drug. Tic-like phenomena have been reported with the use of methylphenidate, but in all but one known case, this too has been reversible with the withdrawal of the drug. Longer term side effects of stimulants also include possible reduction in the rate of weight and height increase. This effect, while somewhat controversial, seems more true of dextroamphetamine than methylphenidate. In view of the limited duration of drug exposure for any child in this protocol, this will b a very unlikely problem.

3. Potential Benefits

The potential benefits of this study are largely in determining whether stimulant medications (in this study methylphenidate and dextroamphetamine) are effective in improving hyperactivity and attentional skills in mentally retarded children over the dosage range employed, and in attempting to determine the most effective drug and dosage range for these benefits. The study also will determine whether these drugs in the dosage ranges employed have any harmful effects on attentional skills, hyperactivity, other behavioral phenomena, or learning in mentally retarded children. Overall, the potential benefits of the study involve establishing useful clinical guidelines for the treatment of hyperactive mentally retarded children with psychostimulant medication.

4. Risk Benefit Relationship

Although there are some risks associated with psychostimulant medication, they are generally not severe in the dosage range employed. The medical supervision in this clinical research center would tend to limit even further potential risks.

Furthermore, given the widespread usage of stimulant and other psychotropic medication in hyperactive retarded children, many of the children on the study may have been exposed to similar stimulants or other psychotropic medications with potentially more serious side effects in the past, or may be exposed to these drugs without the benefits and monitoring implicit in this study, in the future. If stimulant medication proves to be effective for hyperactive mentally retarded children, there will likely be a decreased use of the more dangerous neuroleptic medications with these children. If so, the benefits of this study will be considerable. Additionally, the parameters of effective usage of stimulants (within the dosage range employed) for hyperactive mentally retarded children will have been established.

F. LABORATORY ANIMALS

No laboratory animals will be used in the proposed supplemental project.

G. CONSULTANTS

No consultants other than identified for the current grant are required.

H. CONSORTIUM ARRANGEMENTS OR FORMALIZED COLLABORATIVE AGREEMENTS

There are no consortium arrangements or formalized collaborative agreements.

APPENDIX 2

University of Illinois
at Urbana-Champaign

Institute for Child Behavior
and Development

51 Gerty Drive
Champaign
Illinois 61820

Graduate College

June 20, 1983

415-497-7522

Dr. Jack D. Barchas
Department of Psychiatry
Stanford University Medical Center
Room R-321
Stanford, CA 94305

Dear Dr. Barchas:

This is a proposal for a three-hour panel at the ACNP meeting in San Juan, December 12-16, 1983. It is an interdisciplinary panel involving psychiatrists, psychologists, and an attorney from various backgrounds of university, pharmaceutical firm, psychiatric hospital, and law practice. The panel will discuss the latest findings from three university research projects on assessing TD, the time course of TD, and behavioral supersensitivity associated with TD, as well as a 1982 case, Faigenbaum v. Cohen, in which substantial damages were awarded because of TD to the plaintiff against the State of Michigan which operated the mental hospitals where the plaintiff was treated, and the viewpoints of industry about tardive dyskinesia.

The proposed panelists, their addresses, titles, and very brief summaries of their presentations are listed below.

Tardive Dyskinesia: Prevalence, Time Course, and Recent Litigation
Chair and Discussant
Jonathan Cole, M.D.
Harvard-Boston University Center for
Biobehavioral Studies in the Addictions
McLean Hospital - Oaks Bldg.
115 Mill St.
Belmont, MA 02178

Rated Abnormal Movements in a Study of Retarded Subjects Randomly Assigned to Psychotropic Medication Withdrawal and Control Groups
Robert L. Sprague, Ph.D.
Institute for Child Behavior and Development
51 Gerty Drive University of Illinois
Champaign, Illinois 61820

A group of 194 retarded residents who were scheduled to be given a drug-free holiday under court orders are participating in a systematic psychotropic drug withdrawal study for two years in cooperation with the institution administration. Abnormal movement ratings were made frequently (weekly to every fourth week) on the following groups: medication reduction (N=86); drug control (N=51); and no-drug control (N=57).

called Barchas 08/29/83
merge c̄ John Kane c̄ RLS senior
only $750

called Terry Prewill AC
about non-member
09/22/83
audio-visual 11/15/83

Time Course of Tardive Dyskinesia in the Retarded: Longitudinal Analysis

Stephen E. Breuning, Ph.D.
Department of Psychiatry
Western Pennsylvania Psychiatric Institute
and Clinic
University of Pittsburgh School of Medicine
3811 O'Hara Street
Pittsburgh, PA 15261

Retarded residents who had been on psychotropic drugs for long periods of time were withdrawn from their medication and rated for abnormal movements regularly for a year following medication termination.

Evidence for a Behavioral Analog of Tardive Dyskinesia

C. Thomas Gualtieri, M.D.
Department of Psychiatry
School of Medicine
University of North Carolina
Chapel Hill, North Carolina 27514

Supersensitivity accompanying psychotropic drug withdrawl has been reported in animals, but this is one of the few studies of the phenomenon in humans in a study of systematic psychotropic drug withdrawal with evaluation of behavioral effects as well as tardive dyskinesia.

Faigenbaum v. Cohen

Geoffrey N. Fieger, J.D.
Fieger & Fieger
Attorneys & Counselors at Law
19390 West Ten Mile Road
Southfield, MI 48075

Most of the tardive dyskinesia malpractice cases have been settled out of court, but Faigenbaum v. Cohen is one of the few cases tried in court (12 weeks) involving several defendant physicians and state psychiatric hospitals (Michigan) in which a substantial damage award ($1,000,000 plus interest) was awarded to the plaintiff.

Industry Concerns about Tardive Dyskinesia

Garth Graham, M.D.
Group Director of Medical Affairs
Smith Kline French Laboratories
1500 Spring Garden Street
P.O. Box 7929
Philadelphia, PA 19101

There are many issues surrounding tardive dyskinesia of interest to the pharmaceutical industry: accurate diagnosis, severity of condition, relapse upon withdrawal, proper labeling, and product liability. Many of these issues will be discussed from an industry viewpoint.

According to your 1983 Call for Papers, panels would "typically...last three hours," and, accordingly, this proposed panel has been designed to fit into a half-day format. However, I believe that the considerable interest in tardive dyskinesia and the recent research on large-sample, systematic psychotropic drug withdrawal studies, recent litigation, and viewpoints of industry could easily and profitably be expanded to a full day with more time for questions and answers if the Program Committee was so inclined. If the Committee approves the proposal and if the Committee believes a full day would be useful, based on information obtained and participants attending an NIMH sponsored workshop on tardive dyskinesia at Washington during March 1983, I would be gald to arrange a longer panel with other researchers presenting recent data and NIMH and FDA people presenting different viewpoints.

Sincerely,

Robert L. Sprague
Director

RLS/jm

APPENDIX 3

To: Steve Breuning, Geof Fieger, and Tom Gualtieri

From: Robert L. Sprague

Date: September 26, 1983

Re: ACNP meeting

For the three non-members of ACNP, I enclose a list of the 371 members and 33 drug companies for your information as to whom may be attending the meeting.

Remember, I need your one-page abstract by October 10, 1983.

RLS/sb
Enclosure

University of Illinois
at Urbana-Champaign

Institute for Child Behavior and Development
51 Gerty Drive
Champaign
Illinois 61820

Graduate College

TO: Messrs. Steve Breuning, Jonathan Cole, Geof Fieger, Garth Graham, and Tom Gualtieri

FROM: Robert L. Sprague

DATE: June 20, 1983

RE: ACNP Convention

Enclosed is a copy of a letter I sent to Dr. Barchas, Chair of the Program Committee, for a proposed panel to be held at the next ACNP (American College of Neuropsychopharmacology) meeting in San Juan, Puerto Rico, December 12-16, 1983 at the Caribe Hilton Hotel. If the panel is accepted, I will be back in touch with you about details of registration, travel, etc.

Enclosure

RLS/jm

APPENDIX 24

TIME COURSE OF TARDIVE DYSKINESIA IN THE MENTALLY RETARDED: A LONGITUDINAL ANALYSIS

Stephen E. Breuning, Ph.D.*

Fifty-seven mentally retarded clients (28M/29F) receiving long-term treatment with a single neuroleptic and having no history with other medications (e.g., anticolinergic, antiepileptic) were withdrawn from their medication under placebo and double-blind conditions, maintained drug free, and rated for abnormal movements. Each client was mentally retarded (mean IQ of 40) due to unknown etiology and had no identifiable neurological disorder. The presence of dyskinesias and non-dyskinetic withdrawal symptoms were assessed weekly using the Withdrawal Emergent Symptom Checklist. Assessments began four weeks prior to drug discontinuation and continued for 80 consecutive weeks following drug discontinuation. Assessments were conducted on 45 of the clients at six month intervals for an additional two years (i.e., 45 clients have been followed for 3.5 years). The results showed that 33% showed no withdrawal problems, 35% showed non-dyskinetic withdrawal symptoms (e.g., weight loss), 60% showed dyskinesias by the fourth week post-discontinuation, and 32% persisted in showing dyskinesias after the 16th week post-discontinuation. Only 7% showed dyskinesias prior to drug discontinuation (i.e., maintenance onset). Persistent dyskinesias were primarily (83%) characterized by moderate to severe movements while withdrawal dyskinesias were 65% mild and 35% moderate to severe. The greatest proportion of clients having withdrawal dyskinesias had their dyskinesias cease to occur between the 12th and 16th week after drug discontinuation. Clients having dyskinesias cease to occur after week 16 were primarily those having mild dyskinesias and these disappeared irregularly between weeks 16 and 52. No further change occurred after the 52nd week. Ninety-four (94%) of the clients with moderate to severe persistent dyskinesias showed no changes after week 16.

*John Merck Program for Multiply Disabled Children
Western Psychiatric Institute and Clinic
University of Pittsburgh
School of Medicine
3811 O'Hara Street
Pittsburgh, PA 15213

APPENDIX 5

Jan 82

ROBERT L. SPRAGUE

Tardive Dyskinesia in Mentally Retarded Children, Adolescents, and Young Adults: North Carolina and Michigan Studies

C. Thomas Gualtieri, M.D.,[1] Stephen E. Breuning, Ph.D.,[2] Steven R. Schroeder, Ph.D.,[2] and Dana Quade, Ph.D.[1]

Although neuroleptic drugs are frequently prescribed for behavior control and alleviation of psychiatric symptoms in mentally retarded children, adolescents, and young adults (Lipman, DiMascio, Reatig, & Kirson, 1978; Davis, Cullari, & Breuning, 1982), no systematic or methodologically acceptable studies of the occurrence of tardive dyskinesia (TD) in mentally retarded patients have appeared in the literature (Gualtieri & Hawk, 1980). Two parallel studies of TD and other problems associated with neuroleptic withdrawal were conducted: the North Carolina study (Gualtieri and Schroeder) was primarily concerned with clinical factors associated with TD; the Michigan study (Breuning) was primarily concerned with the course of TD symptoms after neuroleptic withdrawal.

Method

Subjects

Subjects were referred by treating physicians who felt that a trial neuroleptic withdrawal should be a routine part of each patient's clinical management. Inclusion criteria were: a) IQ less than 75, functional diagnosis of mental retardation (American Association of Mental Deficiency criteria); b) stable living environment; c) appropriate educational or workshop placement; d) good general health, with no active neurologic disease, or history of neurologic disorder which might be associated with dyskinesia; and e) continuous neuroleptic treatment of at least 6 months' duration.

North Carolina Study. Thirty-eight subjects (age 5 to 47, mean = 19.4 ± 1.7 [SEM]) were studied at four clinical sites: a psychiatric hospital, a pediatric psychopharmacology clinic, and two residential facilities for the mentally retarded. The mean age at which subjects began neuroleptic treatment was 10.9 (± 1.0) years. The mean duration of treatment was 8.3 (± 6) years, and total lifetime exposure to neuroleptics, expressed in chlorpromazine (CPZ) equivalents (Davis, 1976) ranged from 13.5 to 11,188 grams (mean = 1,046.7 ± 344.3).

N =

Michigan Study. Fifty-seven subjects were studied at the Coldwater Regional Center. Subjects in the Michigan study were older than the North Carolina group ($p < .02$), had higher IQ scores ($p < .001$), and were treated with higher neuroleptic doses immediately prior to withdrawal ($p < .001$) (*see* Table). Because so many subjects in the Michigan group had been treated with neuroleptics for substantial periods of time as outpatients, comprehensive neuroleptic drug histories are not available for this group. All subjects, however, had been treated continuously with neuroleptics for at least 1.3 years prior to entry into this study.

N = 5

[illegible]

Procedure

Subjects received comprehensive neurologic and developmental assessments prior to neuroleptic withdrawal. Special attention was given to neurologic or developmental problems (e.g., cerebral palsy, autism) which might be associated with dyskinetic movements, stereotypies, or psychotic mannerisms which may have anteceded neuroleptic treatment. After baseline evaluation, subjects were withdrawn from neuroleptic drugs, with serial examinations for dyskinesia, behavior change, or nondyskinetic withdrawal symptoms.

North Carolina Study. Subjects were assessed at weekly or biweekly intervals at baseline, during and after withdrawal, and until 8 weeks after complete discontinuance of neuroleptics. The Abnormal Involuntary Movement Scale (AIMS) exam and rating scale were used (Guy, 1976). Subjects who continued to manifest dyskinesia at 8 weeks were subsequently reexamined at monthly intervals. Mean interrater reliability among three physician raters on the AIMS rating scale was 0.83 (0.74-1.00) (Cohen's Kappa).

---

[1] Biological Sciences Research Center, Department of Psychiatry, and the Department of Statistics, University of North Carolina, Chapel Hill, NC 27515.

[2] Department of Psychiatry, Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine, Pittsburgh, PA 15261.

Table

Demographic and Outcome Data

N	N.C. 38	Mich. 57	Total 95
Sex: Male	28	28	56
Female	10	29	39
Age (Yrs) (Mean ± SD)	19.4 ± 10.3	25.7 ± 12.6	
Age Range	5-47	12-71	5-71
IQ	31.2 ± 15.9	40.4 ± 14.8	
IQ Range	9-69	14-74	9-74
Drugs: Thioridazine	28 (74%)	27 (47%)	55 (58%)
Other neuroleptics	10	30	40
Mean Daily Dose (CPZ* equivalents)	239.9 ± 293.8 48.3(SEM)	688.6 ± 310.2 41.1	
Outcome:			
No problems	12 (32%)	19 (33%)	31 (33%)
Withdrawal-related problems	13 (34%)	20 (35%)	33 (35%)
Tardive dyskinesia	13 (34%)	18 (32%)	31 (33%)
Mild	5 (13%)	3 (5%)	8 (8%)
Moderate-severe	8 (21%)	15 (26%)	23 (24%)
Maintenance onset	3 (8%)	4 (7%)	7 (7%)

*Chlorpromazine

57
80
456

80 wks
WESC

Michigan Study! Dyskinetic movements were assessed at weekly intervals at baseline, during withdrawal, and for 80 weeks thereafter. The Withdrawal Emergent Symptom Checklist (WESC) rating scale and examination were used (Engelhardt, 1974), and interrater reliability was 0.79 (Cohen's Kappa).

Results

Four outcome categories were considered according to diagnostic criteria that have been described elsewhere (Gualtieri, Sprague, Breuning, & Campbell, 1981): 1) no problems associated with neuroleptic withdrawal; 2) transient withdrawal problems, that is, withdrawal dyskinesia, nondyskinetic withdrawal symptoms, or acute behavior deterioration; beginning during neuroleptic withdrawal or immediately thereafter, and lasting less than 16 weeks after complete withdrawal; 3) mild TD; and 4) moderate or severe TD. In spite of the clinical differences between the two groups, the outcome of both studies are remarkably similar (*see* Table).

One-third of the total group (*N* = 95) experienced no problems prior to, during, or for at least 8 weeks after neuroleptic withdrawal; one-third experienced only transient withdrawal-related problems; and one-third had TD. Most of the cases of TD were characterized by moderate or severe movements. Of 31 cases of TD, only 7 were apparent while patients were on maintenance doses of neuroleptics. Six of the 7 cases of maintenance onset TD were characterized by dyskinesia that was rated as moderate or severe.

Thioridazine (THD) was the neuroleptic most commonly prescribed in both locations (58% of subjects). There was no association between the use of THD or any other particular neuroleptic and the development of TD.

North Carolina Study

The following were considered in a stepwise regression analysis of variables which might be associated with the development of moderate to severe tardive dyskinesia: location, age, race, sex, age at which neuroleptic treatment was begun, IQ, duration of treatment, total lifetime neuroleptic exposure, mean daily dose, and use of THD as the primary neuroleptic. The single variable that was most highly correlated with the development of moderate or severe TD was total lifetime exposure (analyzed as log of the total lifetime dose, $R^2 = 0.38$ for a one-variable regression). The regression analysis selected three independent variables, total lifetime exposure (log dose), IQ, and the age at which neuroleptic treatment began that were most highly correlated with moderate or severe TD ($R^2 = 0.65$, $F = 18.82$, 3 and 31 *df*), and each independent variable contributed significantly to the regression. Since treatment duration was highly correlated with total lifetime exposure ($r = +0.69$) adding it to the analysis did not increase R^2. None of the other variables contributed significantly to the equation. Nonparametric correlations (Goodman-Kruskal) also showed total lifetime exposure to be the variable most highly correlated with TD ($G = .531 \pm .120$, $p < .0001$).

Michigan Study

Dyskinetic movements were maximal at 4 weeks after neuroleptic withdrawal, when 36 of 57 patients (63%) exhibited symptoms. Dyskinetic movements were noted in 30 patients (53%) at 16 weeks, and in 18 patients (32%) at 52 and 80 weeks. This remission pattern was similar for movements of the tongue, lips and face, and head, limbs, and trunk. Facial dyskinesias which were rated as mild at 4 weeks were more likely to remit, and those which were rated as moderate or severe at 4 weeks were more likely to persist at 80 weeks (chi-square analysis, $p \leq .05$ and $\leq .025$, respectively). Dyskinetic movements which were apparent prior to neuroleptic withdrawal were invariably persistent.

Discussion

Moderate to severe, persistent TD is a cause for concern and a serious problem in mentally retarded children, adolescents, and young adults treated with neuroleptic drugs, a finding that must stand in sharp contrast to the dearth of empirical data to support the clinical use of neuroleptics in this group. The occurrence of TD is, not surprisingly, related to the patient's total lifetime exposure to neuroleptics. Dyskinetic movements that "break through," i.e., that are manifest on maintenance neuroleptic doses, predict a particularly severe and persistent course. However, the large majority of cases of TD — even severe and persistent TD — may not be apparent while patients continue to receive neuroleptic drugs. One may surmise, then, that epidemiologic surveys of TD that do not include trial neuroleptic withdrawal periods will necessarily underestimate the frequency of TD. On the other hand, a substantial number of the dyskinetic movements which arise within 4 weeks of neuroleptic withdrawal will remit spontaneously; such cases are better classified as "withdrawal dyskinesias."

Clearly, although advanced age may increase the risk of TD (Smith & Baldessarini, 1980), youth, at least in combination with mental retardation, does not confer protection from TD. In light of this serious risk, it is noteworthy that very few of the patients in these two samples actually needed to be on neuroleptic medication. In the North Carolina group, only 11 of 38 patients had to return to neuroleptic treatment; in the Michigan group, none returned. When behavior problems following neuroleptic withdrawal did arise, they were usually time limited, or readily controlled using behavioral or programmatic approaches. Many of these behavior problems appeared to be concentrated in the immediate postwithdrawal period, suggesting that a period of behavioral instability occurs following withdrawal. Physicians who withdrew mentally retarded patients from neuroleptic drugs should not take this postwithdrawal behavior deterioration as a mandate to immediately resume treatment with neuroleptics.

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Neuroleptic Serum Levels in Mentally Retarded Boys

James C. Harris, M.D.,[1] Larry E. Tune, M.D.,[1] Michael Kurtz, M.D.[2] and Joseph T. Coyle, M.D.[1]

This is a preliminary report on the measurement of serum neuroleptic levels in mentally retarded children and adolescents. The investigators have measured neuroleptic levels in 60 patients on a variety of neuroleptics (haloperidol, chlorpromazine, trifluoperazine, molindone, thioridazine). However, a summary of neuroleptic blood levels in 9-15 year-old boys taking thioridazine for behavior management is the subject of this report.

Until recently there had been no simple procedure for the measurement of neuroleptic serum activity levels. However, a radioreceptor assay described by Snyder and Creese (1977) based on competition of neuroleptics in plasma or serum for the binding of [^{3}H]-spiroperidol to dopamine receptors may serve this function. The assay measures dopamine receptor blockade and, therefore, detects active metabolites as well as parent drug activity. This is a distinct advantage for thioridazine which has several active metabolites.

Previous reports by Tune, Creese, Depaulo, Slavney, Coyle, and Snyder (1980) and Cohen, Lipinski, Pope, Harris, and Altesman (1980) have demonstrated a correlation between serum levels of neuroleptics and therapeutic response in acutely psychotic patients during an acute episode. Both studies showed poor correlations between oral dosage and serum level.

Myers, Tune, and Coyle (1980) have used this assay to manage schizophrenia in childhood at Johns Hopkins. The current investigators are now studying the use of the radioreceptor assay in the retarded where both thioridazine and haloperidol are approved for use in the management of behavior disorders.

Method

Sixteen moderately to severely retarded 9-15 year-old boys taking thioridazine as a single treatment participated in the study. All are residents in a well-staffed and well-supervised behaviorally oriented institutional setting and are considered to be patients who are the most difficult to manage. Each subject had been on the same dosage of medication for at least 2 weeks.

Five milliliters of blood were drawn from each member of the study population 2 hours after supervised oral administration of the medication to obtain peak blood levels. Specimens were cooled and allowed to clot over a 2-hour period, centrifuged, and the serum frozen at 70° C in glass tubes. Assays were performed in triplicate.

On the day before the blood specimen was obtained, the Sprague Resident Behavior Checklist was completed by the case manager.

---

[1] The Johns Hopkins University School of Medicine and Hospital, Baltimore, MD 21205.

[2] The University of Pennsylvania School of Medicine, Philadelphia, PA 19104.

APPENDIX 6

December 5, 1983

Dr. Stephen E. Breuning
Department of Psychiatry
Western Pennsylvania Psychiatric
Institute and Clinic
University of Pittsburgh School of Medicine
3511 O'Hara Street
Pittsburgh, PA 15261

Dear Steve:

This is a follow-up letter to my Sunday, December 4, 1983 telephone call to your home, and your early call to me Monday morning, December 5, 1983.

This letter is written in the context of my initiating a Panel entitled "Tardive Dyskinesia: Prevalence, Time Course, and Recent Litigation" for the American College of Neuropsychopharmacology (ACNP) December 12 to 16, 1983 annual meeting and my inviting you to present at that Panel in my June 20, 1983 letter to you and the four other proposed participants.

We discussed in our December 5, 1983 phone conversation the discrepancy between the number of subjects (45 of an original 57) repoted in your abstract for the ACNP meeting and the number you now find you have usable data on, namely 25 subjects for one additional 4-month evaluation rather than, as reported in the abstract, 45 subjects with 6-month evaluations for an additional 2 years. I noted the original 57 subjects were from Coldwater Regional Center (CRC), Michigan as reported in Gualtieri, Breuning, Schroeder, and Quade. Tardive dyskinesia in mentally retarded children, adolescents, and young adults: North Carolina and Michigan studies. Psychopharmacology Bulletin, 1983, 19, No. 1, 62-65.

When I called Dr. Neal Davidson of CRC on November 29 and 30, 1983 about this problem, he told me it would be "near a miracle" for the data to be collected in 1981, 1982, and possibly 1983 without his knowing about it. Instead, he told me he did not "know who they are or where they are" in reference to the 45 subjects. I tried to call you about the issue December 1, 1983, but your secretary told me you would be out of town until late December 3, 1983, hence the Sunday call to your home.

As I told you in our December 5 phone call, I believe that you should withdraw the proposed paper, although we agreed to talk about the matter again on Tuesday, December 6, 1983.

Since this serious problem has arisen about the number of subjects, the number of evaluations, and who did the evaluations in your tardive dyskinesia follow-up study, I must request that you give me as soon as possible (within 2 to 3 days) the names or ID numbers of the subjects discussed in your ACNP abstract (either 45 as originally reported or 25 as modified in your December 5 call), their sex, their age at beginning of the study, and the dates of evaluation and the names or initials of the CRC employees (attendants as you indicated in our December 4 call) evaluating them for either the 2-year follow-up as reported in the abstract or the phone call modification of one additional 4-month evaluation.

This information is necessary to verify independently the evaluations and clarify the discrepancies noted above. Also, I want a more complete explanation of why 45 subjects were reported in the abstract, but the number was changed to 25 in your December 5 call, and why the number of evaluations was drastically reduced from 180 (45 subjects x 4 evaluations - every 6 months for 2 years) to 25 (25 subjects x 1 evaluation at 4 months).

Since this problem involves Dr. Neal Davidson and Dr. C. Thomas Gualtieri and since we discussed them in our December 5 phone call, I am sending them a copy of this letter.

Sincerely,

Robert L. Sprague, Ph.D.
Director

RLS/ab
cc: N. A. Davidson, Coldwater Regional Center
C. T. Gualtieri, University of North Carolina

APPENDIX 7

University of Pittsburgh

WESTERN PSYCHIATRIC INSTITUTE AND CLINIC
School of Medicine Department of Psychiatry
Division of Child and Adolescent Psychiatry

December 7, 1983

Robert L. Sprague, Ph.D.
Institute for Child Behavior
and Development
51 Gerty Drive
Champaign, IL 61820

Dear Bob:

This letter is in response to your letter dated 12-5-83. In your letter you request clarification on several points raised during our phone conversations on 12-4 and 12-5.

First, you will find enclosed a copy of the information I have located. This includes (a) age, sex, IQ, medication, medication dosage, and years on current medication for the 24 clients, and (b) baseline, weeks 1, 4, 8, 16, 52, 80, and 96 WESC data. All I could locate was the raw data for the last assessment (96) on these clients and WESC summary data for weeks 1, 4, 8, 16, and 52. Two points warrent comment. First, I have yet to locate the other raw data or the subject indentification code sheet. This information is now three years old and has not been reviewed in some time. I understand the verification problem this leaves us. Second, as you review these summary sheets note that they were developed for another study and used here for economy. Disregard the running-head and reference to nurses. Also, after you receive this information give me a call and I will answer any questions you may have on interpretation.

Second, 45 subjects were identified in the abstract and this was changed to 25 (actually 24-25) in our phone conversation because we were discussing different components of the study. The 45 clients reflect those individuals who were supposedly followed after I left Coldwater. Following a review of the data on these clients and phone calls to Neal and several others it is clear that there are major problems and that these data are not useable. The 25 clients you refer to are the 24-25 clients who I said I was able to get one last evaluation on prior to leaving Coldwater. Thus, the number of evaluations was changed because we were discussing different subgroups of the clients. The 24 clients were ones I had personally assessed and thought might still be presentable at ACNP.

3811 O'HARA STREET, PITTSBURGH, PA. 15213 (412) 624-

However, given that all of the raw data is presently not available and, more importantly, that the subject identification sheet is also not presently available I agree that the data should not be presented at ACNP. Obviously I am hopeful that this information will be located. Further, as I discussed with Tom, I do not believe that any of the data should be published until the subject identification sheet and raw data are located.

Sincerely,

Steve

Stephen E. Breuning, Ph.D.
Assistant Professor

ENCLOSURE

cc: N. Davidson
C. T. Gualtieri
D. Kupfer

APPENDIX 8

4433

ROBERT L. SPRAGUE

An Applied Dose-Response Curve of Thioridazine with the Mentally Retarded: Aggressive, Self-Stimulatory, Intellectual, and Workshop Behaviors—A Preliminary Report[1]

Stephen E. Breuning, Ph.D.[2]

Neuroleptic drugs are frequently prescribed for the mentally retarded in an attempt to suppress a plethora of unwanted behaviors. Surveys spanning the past decade have consistently shown that 40-50% of the institutionalized mentally retarded receive such drugs (*see* Breuning & Poling, in press, for a review). Most recently it has been found that similar use of neuroleptic drugs occurs in community foster homes and group homes for the mentally retarded (i.e., Davis, Cullari, & Breuning, in press). In both institutional and community settings thioridazine is by far the most prescribed neuroleptic with this population, as it accounts for 60-70% of all neuroleptic drug prescriptions.

Despite its wide use, little is known about the therapeutic and contratherapeutic effects of thioridazine. In three recent reviews it was concluded that thioridazine *may* be useful in reducing aggression, general motor activity, and self-stimulation with the mentally retarded (Aman, in press; Breuning & Poling, in press; Ferguson & Breuning, in press). However, these reviews also point out that evidence of therapeutic effect is the exception, not the rule, with thioridazine and the mentally retarded. The issue of therapeutic effect is further confounded by data from several recent reports which suggest that even when there is a reduction in symptomatology, there may well be a concomitant reduction or disruption (increased variability) in adaptive/habilitative behaviors (e.g., Breuning & Davidson, 1981; Breuning, O'Neill, & Ferguson, 1980; Singh & Aman, 1981).

While these findings have consistently been replicated in methodologically sound studies, only one study (Singh & Aman, 1981) has attempted to examine thioridazine effects in a dose-dependent manner. It was found that a low dose of thioridazine was as effective as a much larger dose in controlling self-stimulatory behaviors. The present report represents the initial findings of a study designed to further the findings of Singh and Aman (1981) by assessing the dose-response properties of thioridazine with mentally retarded individuals across four response measures, nine dose levels, and a placebo condition.

Method

N=84

Subjects

The subjects were 84 non-autistic, institutionalized, mentally retarded individuals between the ages of 13 and 27 and with IQs ranging between 34 and 59. Informed consent was obtained for each subject and there were approximately equal numbers of males and females. In total, there were 14 responders and 14 nonresponders assessed for aggressive behaviors, and 16 responders and 16 nonresponders assessed for self-stimulatory behaviors. For the intellectual and workshop behaviors there were 14-14 and 15-15 responders and nonresponders, respectively. Most of the individuals being assessed for the aggressive or self-stimulatory behaviors were also individuals receiving either the intellectual or workshop tasks. There were no individuals assessed on both adaptive measures, and those assessed for aggressive behaviors were not emiting self-stimulatory behaviors and vice versa.

N=3 / 1

Spring-82

16 / 80 wks

Procedure

Each dose and placebo condition lasted for 8 weeks with half of each group (e.g., 7 of 14 responders) receiving conditions in an ascending order and half in a descending order (8-7 or 7-8 for workshop). Because of the clinical nature of the study, these subject assignments were not prepared randomly. Rather, half of the subjects had reached the highest dose as part of clinical treatment and were now withdrawn. The remaining half were determined clinically appropriate for initiation of neuroleptic treatment because of the above-mentioned symptomatology. Double-blind conditions were in effect throughout, as neither

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[1] This study was supported in part by USPHS Grant MH-32206 from the National Institute of Mental Health.

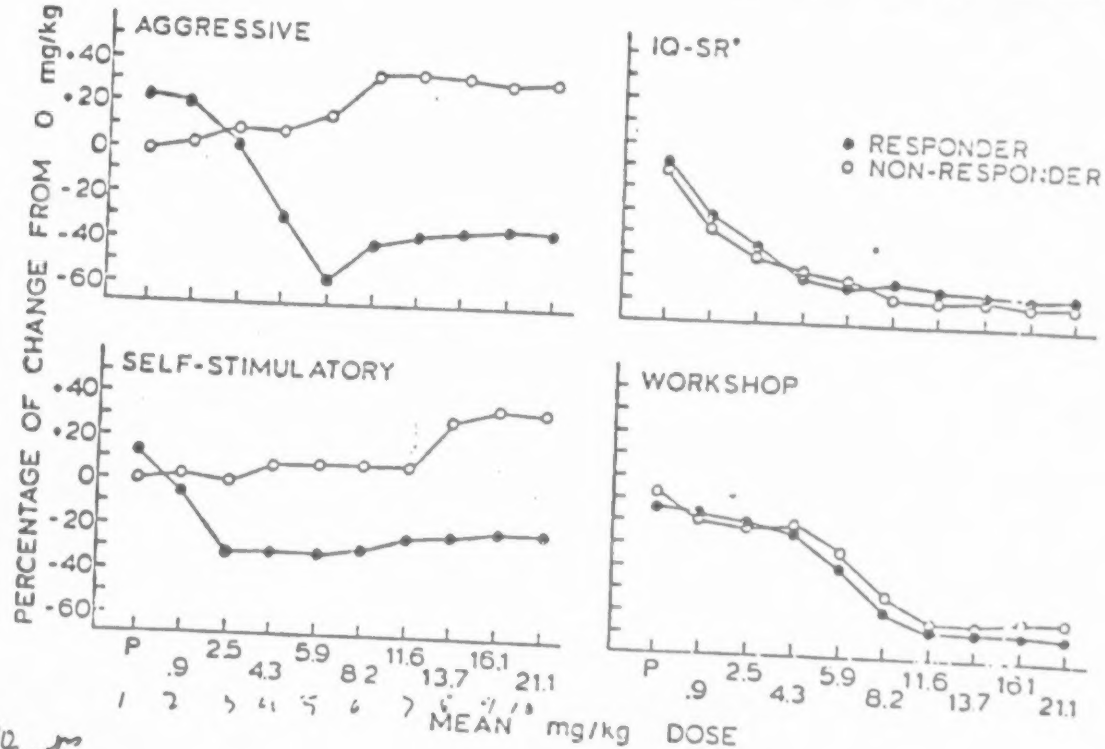
[2] Department of Psychiatry, Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine, Pittsburgh, PA 15261

staff nor subjects were aware of conditions or dose. There were two equal dose administrations daily.

Definitions of aggression and self-stimulation were in observable and measurable terms and recorded by staff in 30-minute intervals, 24 hours per day (*see* Breuning, O'Neill, & Ferguson, 1980). Reliability checks were made by independent observers on a random selection of four 30-minute intervals per day. Mean reliability was 87.4% with a range of 76.3% to 92.4% across days. Intellectual behaviors were assessed using the procedure described by Breuning and Davidson (1981). Briefly, subjects received intellectual testing (Stanford-Binet, Form LM) under conditions where correct responses were reinforced with edible reinforcers selected on an individual basis. Workshop behaviors were assessed using procedures described by Davis, Poling, Wysocki, and Breuning (1981). In short, the number of 15-part coaster bicycle brakes (Bendix RB-2) assembled on an individual basis were counted. Completion of 0-7 of the 15 parts counted as 0 completion, 8-14 of the parts as one-half completion, and 15 parts as one completion.

Results and Discussion

The Figure shows the results from each response measure separately for responders and nonresponders. Data were analyzed using split-plot analyses of variance (one per response measure) with repeated measures and *post hoc* comparisons following Tukey's honestly significant difference (HSD) method (*see* Kirk, 1968).



10 8 wks
80 wks

FIGURE

Percentage of change from the off-drug condition (O mg) plotted separately for responders and nonresponders and each response measure across the placebo condition (P) and nine doses.

Data in the Figure are plotted as percentage of change from the off-drug condition (0 mg) across the placebo (P) condition and nine doses. Data for the aggressive and self-stimulatory behaviors reflect daily frequencies; intellectual behaviors (IQ-SR+) reflect intelligence test scores; and workshop behaviors reflect the number of parts completed per session. Dose levels are plotted as means with no subject having more than a + or − 4% deviation from the mean.

For the responders, a dose of 5.9 mg/kg/day was optimal for reducing aggressive behaviors and a dose of 2.5 mg/kg/day was optimal for reducing self-stimulatory behaviors ($p < .01$). Higher doses had little additional effect except for a loss of behavioral control; i.e., increased frequencies of target behaviors ($p < .01$). For the nonresponders, the frequencies of aggressive and self-stimulatory behaviors showed no substantial changes at the lower doses ($p > .05$) but began to worsen as thioridazine doses increased ($p < .01$). For both responders and nonresponders, there were significant decreases in intellectual and workshop behaviors at even low doses ($p < .01$) and a continued worsening as the dose was increased ($p < .01$). Performance in the IQ-SR+ task was substantially more sensitive to dose changes than with the workshop task. For all response measures and both responders and nonresponders, identical dose effects were obtained regardless of ascending or descending order of conditions ($p > .05$).

The results from this study are clear. Mentally retarded individuals showing a beneficial response to thioridazine treatment (responders) will likely have the greatest suppression of aggressive behaviors occur at a moderate dose (about 6.0 mg/kg/day) and the greatest suppression of self-stimulatory behaviors occur at a fairly low dose (about 2.5 mg/kg/day). Regardless, it is also likely that there will be a concomitant decrease in adaptive/habilitative behaviors. For nonresponders, there may not only be a failure to show suppressed inappropriate behaviors but also a worsening of these behaviors (behavioral toxicity) along with a decrease in adaptive/habilitative behaviors.

There are two additional points worth making. First, preliminary correlational and discriminant function analyses show no significant relationship between psychiatric diagnosis or other possible predictor variables and whether or not an individual was a responder or nonresponder. Second, the equal numbers of responders and nonresponders in this study should not be interpreted to mean that 50% of the mentally retarded receiving neuroleptics will be responders. The reviews cited earlier suggest that only 10-15% of the mentally retarded receiving a neuroleptic will show a beneficial response.

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APPENDIX B
DOCUMENTS RELATING TO UNIVERSITY INVESTIGATIONS

University of Illinois
at Urbana-Champaign

Graduate College

107 Coble Hall
801 South Wright Street
Champaign
Illinois 61820

217 333-0035

April 18, 1984

PERSONAL & CONFIDENTIAL

Ms. Lorraine B. Torres
Associate Director for Extramural Programs
Department of Health and Human Services
National Institute of Mental Health
Rockville, MD 20857

Dear Ms. Torres:

Enclosed please find the final report of the Committee appointed by me to review the allegations of misconduct on the part of Dr. Stephen Breuning, at the University of Pittsburgh, brought to my attention by Dr. Robert Sprague of our Institute for Child Behavior and Development. Supporting materials are attached as appendices.

All parts of the report are confidential. We have not been asked, nor do we expect to share our findings with the University of Pittsburgh until such time as we are informed of the status of the internal investigation being conducted. Then if a request is made and is justified in terms of regulations and law, we will forward a copy to the appropriate authorities there.

I hope you find this report helpful. If there are questions, please feel free to communicate with me or Dean Elaine Copeland.

Sincerely,

Ted Brown

Theodore L. Brown
Vice Chancellor for Research and
Dean, The Graduate College

TLB/EJC/aw

Enclosure

cc: Elaine J. Copeland

University of Illinois
at Urbana-Champaign

Graduate College
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Champaign
Illinois 61820

217 333-0035

CONFIDENTIAL

April 9, 1984

TO: Theodore L. Brown, Vice Chancellor for Research and Dean, The Graduate College

FROM: Douglas Bernstein, Department of Psychology
Robert Linn, Department of Educational Psychology
Martin Maehr, Institute for Child Behavior & Development

VIA: Elaine J. Copeland, EJC Executive Secretary

SUBJECT: Report on the Investigation of an Allegation of Academic Misconduct

What follows is the final report of the Committee to review allegations of misconduct on the part of Dr. Stephen Breuning, a member of the Department of Psychiatry at the University of Pittsburgh, who has collaborated in research with Dr. Robert L. Sprague of our Institute for Child Behavior and Development (ICBD). Enclosed are the answers to your original questions outlined in your charge letter appointing the Committee (Appendix A). Supporting materials are included as appendices.

1. **Is there reasonable basis for suspecting fraudulent scientific practice on the part of Dr. Breuning with or without the possible complicity of other co-workers?**

   On the basis of the December 5th letter Dr. Sprague sent to Dr. Breuning, the December 20th letter Dr. Sprague sent to you and oral comments received by the Committee, there appears to be a reasonable basis for suspecting fraudulent scientific practice by Dr. Breuning. (See Appendices B and C.)

2. **Is there evidence of complicity or willful participation in such fraudulent practice on the part of Dr. Sprague, or any other University of Illinois faculty or staff who have been associated with Dr. Breuning during the course of this research?**

   No, to the contrary, the Committee emphasizes the fact that Dr. Sprague took the initiative and brought this matter to the attention of the appropriate persons even though he was fully aware that his allegations might jeopardize future funding of his National Institute of Mental Health (NIMH) grant. In general, Dr. Sprague appears to have behaved in accordance with the Campus Policy on Academic Fraud and Misconduct and good professional practice. (See Appendix C.)

3. **Did Professor Sprague exercise reasonable diligence and take appropriate actions in notifying responsible officials at the University of Pittsburgh, the National Institute of Mental Health, and elsewhere, of his findings and suspicions?**

CONFIDENTIAL

Yes. A review of Professor Sprague's letters and the personal notes of Associate Dean Elaine Copeland and the Campus Policy of Academic Fraud and Misconduct (see Appendices B, C, D and E) indicates that Professor Sprague was judicious in bringing this matter to the attention of appropriate administrative officials. He initially discussed his concerns with Dean Elaine Copeland, Graduate College liaison for the Institute for Child Behavior and Development (ICBD), and with Associate Vice Chancellor Linda Wilson, Secretary to the University of Illinois Research Board. At an appropriate time he apparently also presented his concerns to Dr. Breuning and formally notified the apropriate authorities at the University of Illinois, at NIMH, and at the University of Pittsburgh.

As a result of a telephone conversation between Ms. Lorraine Torres and Dean Copeland, you asked the Committee to address the question of the impact of Dr. Breuning's data on the research and publications of Dr. Sprague. In response to this request, Dean Copeland requested the information found in Appendix E. The Committee reviewed these materials, met to discuss their evaluations and the Committee concluded the following:

1. The data used in Dr. Sprague's research were independent of those of Dr. Breuning.
2. There was no indication that the research conclusions of Dr. Sprague have been affected by Dr. Breuning's data.
3. Thus, the Committee concluded that there was no impact of Dr. Breuning's data on Dr. Sprague's work.

In summary, the Committee believes there is reasonable cause for a thorough investigation. It is assumed that this investigation will be conducted by the University of Pittsburgh. We believe that the results of that investigation should be provided to you.

EJC/aw

Enclosures

University of Illinois
at Urbana-Champaign

Graduate College
107 Coble Hall
801 South Wright Street
Champaign
Illinois 61820

217 333-0035

APPENDIX A

CONFIDENTIAL

December 28, 1983

CONFIDENTIAL

TO: Professor Douglas Bernstein
Professor Robert Linn
Professor Martin Maehr

FROM: Theodore L. Brown Ted Brown

SUBJECT: Investigation of a Potential Instance of Academic Misconduct

Professor Robert L. Sprague, Director of the Institute for Child Behavior and Development, has reported to me an instance of suspected fraudulant scientific practice on the part of a close colleague of his, a Dr. Stephen E. Breuning, of the Department of Psychiatry, Western Pennsylvania Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine, 3811 O'Hara Street, Pittsburgh, PA 15261. Dr. Breuning has been partially supported on a grant from the National Institutes of Mental Health, MH 32206, and he has received two subcontracts funded by this grant to the University of Pittsburgh, in 1982-1983 and 1983-1984. Dr. Sprague has outlined to me in a lengthy letter, dated December 20, 1983, the various evidences upon which he bases his conclusion that fraudulent scientific practice may have occurred.

I am asking you to serve as a Committee of three, with Associate Dean Elaine J. Copeland as Executive Secretary, to carry out an investigation of this instance of suspected fraudulent practice. It is vitally important to the interest of the University of Illinois, and to Professor Sprague, that this matter be evaluated as rapidly as possible.

I ask the Committee to make the following determinations:

1. Is there a reasonable basis for suspecting fraudulent scientific practice on the part of Dr. Breuning, with or without the possible complicity of other co-workers?

2. If the answer to this first question is yes, is there any evidence of complicity or willful participation in such fraudulent practice on the part of Dr. Sprague, or any other University of Illinois faculty or staff who have been associated with Dr. Breuning during the course of this research?

3. If the answer to the first question is yes, did Professor Sprague exercise reasonable diligence and take appropriate actions in notifying responsible officials at the University of Pittsburgh, The National Institutes of Mental Health, and elsewhere, of his findings and suspicions?

I believe that the Committee can best begin by meeting with Professor Sprague, to learn from him in detail the basis of his concerns. You will also wish to meet with other U of I faculty or staff who have had contacts with Dr. Breuning in relationship to the suspected research activities. I presume that during the time you are undertaking your investigations there will be a concurrent investigation at the University of Pittsburgh. The Committee will be kept informed of the progress of that and other investigations as information becomes available to us.

In addition to a report from the Committee that deals explicitly with the matters raised above, I would value advice from the Committee as to how the University might best proceed to minimize any adverse impact, should the fraudulent practices which Professor Sprague fears have occurred be substantiated by more detailed inquiry.

Finally, I ask that you conduct these activities with the utmost attention to confidentiality. Other than contacts with additional University of Illinois faculty and staff as are required in order to carry out the investigation, these matters should not be discussed with anyone other than Professor Sprague, Dean Copeland or myself. All written materials relating to this matter should be kept in a secured place, perhaps a locked safe or at your individual homes.

An investigation of this kind is for all of us an unpleasant matter. I very much appreciate your willingness to undertake this important and sensitive responsibility on behalf of the University.

TLB/aw

cc: Elaine J. Copeland✓

APPENDIX B

CONFIDENTIAL

December 5, 1983

Dr. Stephen E. Breuning
Department of Psychiatry
Western Pennsylvania Psychiatric
   Institute and Clinic
University of Pittsburgh School of Medicine
3811 O'Hara Street
Pittsburgh, PA 15261

Dear Steve:

This is a follow-up letter to my Sunday, December 4, 1983 telephone call to your home, and your early call to me Monday morning, December 5, 1983.

This letter is written in the context of my initiating a Panel entitled "Tardive Dyskinesia: Prevalence, Time Course, and Recent Litigation" for the American College of Neuropsychopharmacology (ACNP) December 12 to 16, 1983 annual meeting and my inviting you to present at that Panel in my June 20, 1983 letter to you and the four other proposed participants.

We discussed in our December 5, 1983 phone conversation the discrepancy between the number of subjects (45 of an original 57) repoted in your abstract for the ACNP meeting and the number you now find you have usable data on, namely 25 subjects for one additional 6-month evaluation rather than, as reported in the abstract, 45 subjects with 6-month evaluations for an additional 2 years. I noted the original 57 subjects were from Coldwater Regional Center (CRC), Michigan as reported in Gualtieri, Breuning, Schroeder, and Quade. Tardive dyskinesia in mentally retarded children, adolescents, and young adults: North Carolina and Michigan studies. Psychopharmacology Bulletin, 1983, 19, No. 1, 62-65.

When I called Dr. Neal Davidson of CRC on November 29 and 30, 1983 about this problem, he told me it would be "near a miracle" for the data to be collected in 1981, 1982, and possibly 1983 without him knowing about it. Instead, he told me he did not "know who they are or where they are" in reference to the 45 subjects. I tried to call you about the issue December 1, 1983, but your secretary told me you would be out of town until late December 3, 1983, hence the Sunday call to your home.

As I told you in our December 5 phone call, I believe that you should withdraw the proposed paper, although we agreed to talk about the matter again on Tuesday, December 6, 1983.

CONFIDENTIAL

Dr. Stephen E. Breuning
December 5, 1983
Page Two

Since this serious problem has arisen about the number of subjects, the number of evaluations, and who did the evaluations in your tardive dyskinesia follow-up study, I must request that you give me as soon as possible (within 2 to 3 days) the names or ID numbers of the subjects discussed in your ACNP abstract (either 45 as originally reported or 25 as modified in your December 5 call), their sex, their age at beginning of the study, and the dates of evaluation and the names or initials of the CRC employees (attendants as you indicated in our December 4 call) evaluating them for either the 2-year follow-up as reported in the abstract or the phone call modification of one additional 4-month evaluation.

This information is necessary to verify independently the evaluations and clarify the discrepancies noted above. Also, I want a more complete explanation of why 45 subjects were reported in the abstract, but the number was changed to 25 in your December 5 call, and why the number of evaluations was drastically reduced from 180 (45 subjects x 4 evaluations - every 6 months for 2 years) to 25 (25 subjects x 1 evaluation at 4 months).

Since this problem involves Dr. Neal Davidson and Dr. C. Thomas Gualtieri and since we discussed them in our December 5 phone call, I am sending them a copy of this letter.

Sincerely,

Robert L. Sprague, Ph.D.
Director

RLS/sb
cc: N. A. Davidson, Coldwater Regional Center
C. T. Gualtieri, University of North Carolina

APPENDIX C

CONFIDENTIAL

December 20, 1983

Dean Theodore L. Brown
Graduate College
107 Coble Hall

Dear Ted:

It is with regret and considerable personal sorrow that it is necessary to write to you about suspected fraudulent scientific practices of a close colleague, Dr. Stephen E. Breuning (Department of Psychiatry, Western Pennsylvania Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine, 3811 O'Hara Street, Pittsburgh, PA 15261, telephone number 412-624-2331). Steve has been partially supported by my grant MH 32206, and he has received two subcontracts funded by this grant to the University of Pittsburgh in 1982-83 and 1983-84. The facts are listed below in outline form to aid in statement of the situation and details which are sometimes technical.

A. Chronology of events

1. On September 22 and 23, 1983, I visted Steve as is my practice to visit routinely the sites where collaborative research is being conducted as part of my grant. Steve and Vicky Davis graciously invited me to visit their new home in a Pittsburgh suburb and to stay overnight with them. While discussing research the Thursday evening of September 22, I mentioned the difficulty we were experiencing in obtaining high interjudge reliability on the tardive dyskinesia (TD) ratings using the Dyskinesia Identification System - Coldwater (DIS-Co) at mental retardation facilities in Minnesota where my research is being conducted. Vicky responded that interjudge reliability was not a problem in her TD studies because she was obtaining 100% reliability with nurses as raters. Although I did not say much in reply. I was shocked and immediately alerted to the possibility of unsupportable data because I do not think it is possible for anyone, no matter how skilled a researcher, to obtain perfect agreement between two raters in an area as complex as judging abnormal movements associated with TD. The next day further doubts were aroused when Steve and I discussed his responder and non-responder data and the near perfect distinction in his various measures between these two categories of response to psychotropic drugs.

2. Steve kindly gave me a copy of his first Progress Report on his grant at the University of Pittsburgh entitled, "Stimulant Drugs with the Mentally Retarded" MH/HD 37449 (Appendix 1) which covered the period from July 1, 1982 to June 30, 1983 (although 1984 is listed on page 4 of the Report, the date seems to be a mistake). Because of the events mentioned in A.1. above, I read the report very carefully on the plane back home. More suspicions about his data were aroused, only one of which will be mentioned. If the report covers only one calendar year, then 261 working days (365 days minus 104 weekend days) are available not subtracting holidays.

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Dean Theodore L. Brown
December 20, 1983
Page Two

Table 1

Facts on Studies, Number of Subjects, and Length of Studies Reported in MH/HD 37449 Progress Report

Study Number	Subjects	Sessions per Subject	Total Sessions	Length of Study in Days
1	12	4	48	?
2	11	5	55	?
3	13	7	91	49
4	24	7	168	49
5	14	9	126	63
6	12	9	108	63
7	13	7	91	49
Totals	99	48	687	273

Assuming that the 7 reported studies were conducted consecutively (it seems unlikely that two or more of the studies could not be conducted concurrently considering the limitations of the subject population and availability of experimental rooms), then it is difficult to understand how 273 study days (the total number of days it took to complete 5 studies not counting studies 1 and 2) could be completed in 261 working days. Moreover, these calculations do not take into account the ordinary circumstances of life that, at least, I am always plagued with in an experiment: subjects who miss appointments, research assistants who become sick and miss work, equipment breakdowns, etc.

3. As soon as possible after arriving home, I called together a few close colleagues who were familiar with Steve and his research. On September 26, 1983, these three people from the Institute for Child Behavior and Development met with me in my office to discuss problems with his data: Dr. Esther K. Sleator, a pediatrician who met Steve in 1979 when he first visited the Institute and who has read his papers; Ms. Rina K. Ullmann, a Research Associate who first introduced me to Steve and who was quite familiar with his rsearch; and Mrs. Janis C. Rusch, a Research Assistant who had complained to me a number of months previously about Steve's papers and articles being "too good" and "too consistent" to be true. Since my suspicions were based on "soft information," we discussed what should be an appropriate course of action.

4. As a first step to clarify the situation, I began to look more closely at Steve's writings and closely inspect the reported results. During this time one of his grant applications to the March of Dimes with Dr. Patrick Achles, a Post Doctoral Fellow at the University of Pittsburgh, was sent to me for review, and I declined to review it.

5. On November 7, 1983, Dr. Michael G. Aman (Department of Psychiatry, School of Medicine, University of Auckland, Private Bag, Auckland, New Zealand, telephone number 695-775-780) visited me, and the topic of Steve's research was mentioned in the context that Mike was obtaining different results with stimulant medication than Steve had reported. I indicated Steve's dose response data with stimulant medication using teacher rating scales showed a different pattern than I and other researchers had obtained. The next three days I

visited institutions in Minnesota at the request of the Court Monitor in the Welsch case and heard more disturbing comments about Steve's data and activities.

6. After meeting with Esther Sleator and Rina Ullmann again on November 14, 1983, it was decided to contact Dr. Ronald S. Lipman (Johns Hopkins Hospital, B6, Phipps Clinic, 600 North Wolfe Street, Baltimore, MD 21205, telephone 301-955-3065) for a number of reasons: he was a scholar familiar with the area; he was retired from the Psychopharmacology Research Branch of the National Institute of Mental Health (NIMH) and was quite knowledgeable about their procedures; since he was no longer in the employment of NIMH, the phone call could not be construed as an official complaint at that time to the agency, and I was reluctant to make such an official complaint due to the "softness" of the evidence; and he was independent of the situation and could, thus, give unbiased advice. I called him on November 15, 1983. He subsequently requested my permission to share confidentially the information with Dr. Mitchell Balter (Applied Therapeutics and Health Practices Program, National Institute of Mental Health, Room 9C-23 Parklawn Building, 5600 Fishers Lane, Rockville, MD 20852, telephone number 301-443-3946) for his advice and counsel, and I agreed on the basis that the information would be kept confidential and not perceived as an official complaint at that point.

B. ACNP abstract

1. On June 20, 1983 I invited Steve and four other people to participate in a proposed symposium to be presented at the annual meeting in December of the American College of Neuropsychopharmacology (ACNP); a copy of the letters are in Appendix 2. The proposal was accepted, although Dr. Garth Graham subsequently declined to speak.

2. Although I requested abstracts of their papers by October 10, 1983 (Appendix 3), Steve sent me a copy of his abstract (Appendix 4), which he mailed directly to ACNP sometime in November. Note carefully that his description of the follow-up study in the abstract states there were 45 subjects followed for 2 years with 6-month assessments.

3. I did not realize the possibility of a discrepancy between what was written in the abstract and what I knew was possible at Coldwater Regional Center, Coldwater, Michigan where the follow-up study was conducted until November 28, 1983 when I called Dr. C. Thomas Gualtieri (Department of Psychiatry, School of Medicine, University of North Carolina, Chapel Hill, NC 27514, telephone number 919-966-5161) about the first of three programs on tardive dyskinesia which CBS News broadcast on the evening news that day; both Tom and I had talked to CBS News extensively about the program. Tom mentioned that Steve would be presenting 2 years of follow-up TD data at ACNP, and I immediately realized there might be a problem when Tom made that comment.

4. The next day, November 29, 1983, I again carefully checked the abstract and numerous papers written by Steve. It became apparent that the follow-up study reported in the abstract was a continuation of the published study of Gualtieri, Breuning, Schroeder, and Quade. Tardive dyskinesia in mentally

retarded children, adolescents, and young adults: North Carolina and Michigan studies." Psychopharmacology Bulletin, 1982, 18, No. 1, 62-65 (Appendix 5). The Gualtieri, Breuning et al paper clearly stated the subjects were from Coldwater Regional Center (see page 62 of Apeudix 5). Since I had visited Coldwater Center about three times after Steve left there about January 1, 1981 for a position at the University of Pittsburgh, I was aware that it was highly unlikely that 45 subjects could be followed for 2 years after his departure. To check this further on November 29, 1983, I called Dr. Neal A. Davidson (Director of Psychological Services and Behavioral Treatment Program, Coldwater Regional Center for Developmental Disabilities, P. O. Box 148, Coldwater, MI 49036, telephone number 517-279-9551) who handled TD evaluations for Coldwater Center. He told me it would be "near a miracle" for the data to be collected without his knowledge and that he did not know who "they [the subjects] are or where they are." To be absolutely certain, I called him again the next day, November 30, 1983 to re-confirm his earlier statements.

5. I tried to call Steve to confront him with the discrepancy between the abstract statements and Neal's statements, but I could not reach him since he was out-of-town until Sunday, December 4, 1983 when I called him at home. My phone call and questions about the discrepancy surprised Steve, to say the very least. I indicated I would send him an express letter (Appendix 6) the next day, December 5, 1983, requesting supporting documentaion on the existence of the subjects and their evaluations.

6. A few minutes after 8:00 a.m. Monday, December 5, 1983, Steve called me; he seemed very upset. He indicated he had worked all night after my call and that he could not find all the supporting documentation which I requested. He further stated he could only find 25 subjects who were evaluated once at 96 weeks or 4 months following the 80-week study of Gualtieri, Breuning et al. I said my express letter would be on the way to him within hours. When he asked me about presenting the paper at ACNP on December 12, 1983, I said he should not.

7. Because problems with the follow-up study raised questions about the Gualtieri, Breuning et al paper and because Tom was a member of the ACNP symposium and planning to present further data collected in collaboration with Steve, I called Tom on November 30, 1983 to alert him confidentially to the potential problem and likely possibility that I would block the presentation of Steve's paper at ACNP on December 12, 1983.

8. On Thursday, December 8, 1983, I received Steve's express letter to me with part of the requested documentation (Appendix 7). Note that the subject identification code which translates the identification numbers to the subject names has not been located and that only 24 subjects were evaluated once at 96 weeks.

9. I was out-of-town part of December 9 and 10, 1983 and did not talk to Steve by phone on those days, although we talked by phone daily or twice a day since my December 4, 1983 phone call to his home. However, I reached him at home, Sunday, December 11, 1983. I indicated I received his December 7, 1983 letter (Appendix 7) but that my question as to why he reported in the abstract

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45 subjects with 2-years of follow-up and then reduced it to 24 subjects with one 4-month evaluation was not answered. A number of questions about the supporting documentation was raised, only one of which will be mentioned. Steve stated he had personally examined all 24 of the subjects (see also Appendix 7). I asked him again if he examined all 24 of the subjects before he left Coldwater Center, and he said "yes." Then while flipping through the copies I asked him how he could have examined subject 10-21 (I added the first number and dash to the ID number for my convenience) on January 5, 1981 when he had left for Pittsburgh before that date. He stated he probably did not leave until January 20, 1983. Again, another example of a discrepancy which is extremely disconcerting to me, and, for me at least, casts considerable doubt on the authenticity of the remaining 24 subjects.

10. I did not permit Steve to present his paper at ACNP, although he requested to present a modified paper with 24 subjects.

C. Implications for other resarch

1. It is my understanding that Tom Gualtieri has requested supporting documentation for the data reported from Michigan in the Gualtieri, Breuning et al paper (Appendix 5) and that none of the raw data is available.

2. If raw data is missing for the Gualtieri, Breuning et al study, then it seems likely that data may be missing for Breuning, S. E. An applied dose-response curve of thioridazine with the mentally retarded: Aggressive, self-stimulatory, intellectual, and workshop behaviors - A preliminary report. Psychopharmacology Bulletin, 1982, 18 (1), 57-59 paper (Appendix 8) since it is very likely that there was considerable overlap between the subjects of the two studies. However, I have not, at this time, investigated this possibility.

3. The question, of course, arises as to how much supporting documentation is available for Steve's series of studies.

D. Information given to the University of Illinois and other universities

1. When I ws talking to Associate Dean Elaine J. Copeland on September 27, 1983 about another matter of a faculty member's impending absence for cancer treatment, I mentioned to Elaine my trip to the University of Pittsburgh September 22-23, 1983 and my initial suspicions.

2. Elaine mentioned the possible problem to Dr. Linda S. Wilson, and I talked briefly to Linda on September 28, 1983.

3. You will recall I mentioned the problem to you when you attended the Institute faculty meeting on November 3, 1983.

4. While attending the ACNP meeting, I talked to Dr. David J. Kupfer (Department of Psychiatry, Western Pennsylvania Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine, 3811 O'Hara Street, Pittsburgh, PA 15261, telephone number 412-624-2353) on December 14, 1983. He is Steve's administrative superior at the University of Pittsburgh. He

indicated he would appoint a committee to investigate the matter as soon as he returned to his office on December 21, 1983 and call me about the committee the same day.

5. Also, while at the ACNP meeting, Dr. Morris A. Lipton (Biological Sciences Research Center, School of Medicine, University of North Carolina, Chapel Hill, NC 27514, telephone number 919-966-1456), whom I have known for a long time and who is the administrative superior of Tom Gualtieri, stopped me and asked my impressions of the Breuning affair. I gave him a very brief summary of the above details. His main response was to sadly shake his head.

6. As soon as I returned to the campus from the ACNP meeting, I called Ms. Natalie Reatig (Project Office for my grant MH32206, Social Science Analyst, Pharmacologic and Somatic Treatments Research Branch, National Institute of Mental Health, Room 10C-05 Parklawn Building, 5600 Fishers Lane, Rockville, MD 20857, telephone number 301-443-3526) on December 16, 1983. She stated NIMH would appoint a committee to investigate, but the action probably would not be taken until January after the holiday season. She requested that I write her a letter presenting the details of the situation, and I am preparing such a letter very similar to this one I have written to you.

7. Since several administrators and researchers at several different institutions already have information about the incident and since there is a potential for many other people to be involved (Steve has co-authored at least 39 papers, book chapters, and books with 16 people in 4 institutions since 1980), there is a great potential for rumor and misinformation to develop as well as public disclosure in the media.

8. To the best of my knowledge, I am the first person among his numerous colleagues and co-authors to bring suspicions and evidence to the proper officials. Therefore, I request you appoint an ad hoc committee as suggested in the draft copy of the Policy on Academic Fraud and Misconduct to investigate my role and actions in the matter. Frankly, I am very concerned that rumor will implicate me in this affair, and I most definitely would like to have an official report from the University of Illinois to counteract such rumors.

Sincerely,

Robert L. Sprague
Director

RLS/sb
Enclosures
cc: [illegible] J. Copeland ✓

APPENDIX D CONFIDENTIAL

Academic Integrity

Suggested procedures: Developed in consultation with Associate Vice Chancellor Linda Wilson.

1. Discussion with the investigator. Frame questions to validate what he suspects. (a) observe data, (b) are human subjects involved; is anyone at risk due to misconduct?. (Telephoned R. Sprague 9/29/84 in the evening.) No subjects at risk but indirectly the public at large may be affected.

2. (a) Documentation of all discussions and observations.

   (b) Establish whether there should be an investigation. Submit a formal document to Theodore Brown.

   (c) Include in the document:

      1. Type of research
      2. What grants
      3. Date when he became concerned
      4. When he talked with others
      5. Nature of the allegation
      6. Reasons for suspicion
      7. Are human subjects involved?
      8. What institutions?
      9. Sources of funds
      10. Other research workers, other collaborators active in the research
      11. Direct supervision of the accused

3. Consult Legal Counsel

4. (a) If suspicion justified, contact the Provost at the other institution

   (b) 1. Determine how to submit documentation
      2. Determine whether there is a mechanism already in place
      3. What is the role of the University of Illinois at this point? Should we ask only for a report of what happened? Should we ask to have a peer from Illinois who is not involved in the research to serve as a part of the review panel (team)?

[illegible] CONFIDENTIAL

Personal Notes:

E. J. Copeland

September 27, 1983

1. Robert Sprague telephoned on 9/27/83 to indicate that he had a concern. He also called Linda Wilson on that date.

2. I initially thought the person under suspicion was a colleague on this campus.

3. The subject under investigation is at another university.

4. Robert Sprague initially recommended him for the position. The subject under investigation was a postdoctoral student, supervised earlier by Professor Sprague.

September 29, 1983

5. I met with Linda Wilson to discuss procedure.

6. I called Robert Sprague 9/29/83 during the evening to determine whether there were subjects at risk.

Requested Grant Number:

863-2039 MH 32-206 1982-83

Subcontractor

A grant is now in. A decision is expected on October 21, 1983.

November 17, 1983

Discussed with Professor Sprague his concern regarding falsification of data. He indicated that the portion of the proposal submitted by the researcher was not funded. Professor Sprague will continue to attempt to obtain raw data in order to run tests.

December 5, 1983

Robert Sprague called to inform me of the developments in the joint research effort. He was concerned that a paper with questionable subjects and results was going to be delivered at a national conference. He suggested a meeting to discuss action. He called the individual to express his concern.

A copy of a letter to the researcher was sent December 5, 1983.

I met with Dean Brown and Associate Dean Linda Wilson at 4:30 on December 5, 1983 to discuss our responsibility to notify the other institution. When Professor Sprague returns from the meeting to be held December 12-16, 1983 we will meet with the Legal Counsel here to discuss procedure.

December 6, 1983

Met with Linda Wilson to indicate that a meeting will be scheduled when Professor Sprague returns.

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December 7, 1983
Telephone call from Robert Sprague, Prof. Breuning called Sprague and Sprague indicated that Breuning appeared depressed and said that Breuning could not find the data. Sprague is concerned about his safety. Sprague indicated that he believed the data was fabricated and asked Breuning to inform his immediate supervisor.

December 7, 1983
Discussed with Linda Wilson. We should discuss with Dean Brown when he returns on Thursday December 8, 1983.

December 8, 1983
Bob Sprague telephoned. Breuning indicated that he informed his supervisor and offered to resign. Supervisor did not accept resignation. Bob plans to contact supervisor at a meeting next week.

December 8, 1983
Meeting with Dean Brown. Call Jack Kamerer and stop flow of money to Pittsburgh.

December 14, 1983
Met with Sprague. He discussed the case with supervisor at Pittsburgh. A committee will be set up to investigate. I suggested that Sprague send confidential letter to Dean Brown describing his reasons for concern in detail. A meeting with Brown and Sprague is scheduled for Thursday, December 22, 1983 at 2:00 p.m.

December 22, 1983
Suggest meeting with Tim Madigan for legal consultation.

December 28, 1983
Committee was formed on December 28, 1983. Members are:
1. Professor Douglas Bernstein, Department of Psychology
2. Professor Robert Linn, Department of Education
3. Professor Marty Maehr, Institute for Child Behavior & Development

EJC/aw

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DRAFT -- 12/83

POLICY ON ACADEMIC INTEGRITY

Preamble

The academic community has become increasingly concerned about instances of serious breaches of conduct within its ranks. While the number of cases discovered is small in relation to the number of scholars on campuses across this country, any academic misconduct is repugnant to ideals of academic integrity. Therefore incidents involving misconduct in research have prompted numerous professional bodies including the Association of American Universities to suggest guidelines for the maintenance of standards of integrity in research and publication.

In its report the Committee on Academic Integrity of the AAU recommends that:

> "All institutions prepare policies which state clearly the expectations for high standards of ethical behavior of those involved in research, the procedures for dealing with suspected deviations from intellectual honesty, and available sanctions. These policies and procedures must be consistent with the institution's policies on academic governance, freedom, responsibility and due process, as well as with legal restraints."

Concerned about this matter, and in response to the AAU report, Theodore L. Brown, Vice Chancellor for Research and Dean of the Graduate College, UIUC, sought the advice of the Senate Council. The Council referred the question to the Senate Committee on General University Policy which in turn requested the appointment of an ad hoc committee within the Graduate College to address the issue.

Rather than dealing with all the numerous kinds of potential faculty misconduct--capricious grading, excessive absence from classes, etc.--the committee was specifically charged with proposing ways the UIUC campus should deal with allegations of misconduct in scholarship and research. The committee charge was broad enough, however, to include not only a statement on policy and procedures for dealing with misconduct, but also to involve it in the broader issue of the prevention of fraud by fostering a climate of academic integrity on the UIUC campus.

The committee is aware that many professional associations have ethical codes or guidelines for the conduct of research within their disciplinary areas and that individual researchers are expected to adhere to these guidelines in their respective research endeavors. Violations of such guidelines and ethical codes are a matter for peer review and censure, and may, in some instances, also become grounds for University disciplinary action as outlined in this document.

The ad hoc committee assumes that a positive climate for the exchange of information among scholars is an important factor in the maintenance of academic integrity on campus. The encouragement of intellectual honesty at all levels within the academic community is the foundation that fosters such a climate. Undergraduate and graduate researchers are the principal investigators of the next generation. The values they are exposed to in day-to-day interactions within research groups will influence the quality and the level of integrity in research for future generations. Thus, a continuing tradition of academic integrity depends on the scholars and researchers on the campus today.

The high level of research quality and academic integrity that this campus has traditionally enjoyed will be maintained primarily by the encouragement of intellectual honesty, disapproval of the "success at any cost" syndrome, the maintenance of fair and open professional relationships and the generous assignment of credit or acknowledgment of work completed by others. At the same time even an occasional departure from standards of integrity by members of the academic community makes it necessary to consider policy and procedures for investigating possible breaches of academic integrity. Appropriate procedures need to be in place in case incidents of misconduct do arise, no matter how rarely. The following policy is offered for consideration and discussion.

Policy

The University of Illinois is dedicated to learning and research, and hence is committed to truth and accuracy. Integrity and intellectual honesty in scholarship and scientific investigation are, therefore, as at any university worthy of the name, of paramount importance. It is the responsibility of faculty and staff to maintain high ethical standards of professional integrity.

The University of Illinois considers any of the following to be a major breach of professional standards of competence and responsibility:

1. Fabrication or falsification of data, including intentionally misleading selective reporting.
2. Plagiarism, abuse of confidentiality with respect to unpublished material, flagrant violations of accepted standards regarding submission and publication of scholarly works, and other misrepresentations of originality.
3. Irresponsible failure to comply with research regulations, such as those applying to human subjects, laboratory animals and standards of safety.

Prevention

The University of Illinois concurs in the Association of American Universities Report of the Committee on the Integrity of Research which states in part:

> "Nothing can substitute for a pervasive attitude of intellectual honesty. . . . At a minimum, . . . standards include: open communication, submission of work for peer review, avoidance of conflict of interest, and commitment to self-regulation. The encouragement of intellectual honesty is not the responsibility of

> a few but must be accepted by all persons in the university . . . It is our opinion that a positive attitude of intellectual honesty does more to prevent dishonesty than any other single factor."

Potential problems of questionable conduct may largely be forestalled within the academic community by appropriate attitudes and preventive practices including:

1. Constant concern by individual scholars for quality and appropriate regard for the extent of personal involvement in work for which individuals accept credit or responsibility. As is more particularly stated in the Association of American Universities Report on Integrity of Research:

   > "A climate of integrity should include generosity in recognizing the accomplishments of others. Adequate citation of the contributions of [others] . . . is especially important. Publications should list as authors only those who contributed significantly to the research, are prepared to stand behind the conclusions, and have reviewed the manuscript carefully."

2. Instruction in the practices and standards of professional integrity and quality, including those applicable to specific fields and professions, as a normal component of education and training for research.

3. Careful scrutiny of staff and their previous work for scholarly integrity at times of hiring and advancement. Informed review and qualitative evaluation should be a normal incident of research and scholarship and its recognition.

4. Wide dissemination within the University of its policies regarding scholarly integrity together with information about consequences of their breach.

5. A clear and precise statement by the University of procedures to be followed in case of possible misconduct, including prompt action and appropriate safeguards for both those whose conduct is in question and those who report the questioned conduct. A set of procedures is proposed below.

Procedures in Cases of Suspected Misconduct

1. Any member of the university community who becomes aware of an apparent instance of fraud or other academic misconduct relating to research or scholarship has the responsibility to try to resolve the issue, if possible, in consultation with those directly involved. If consultation is inappropriate or unsuccessful, it is incumbent upon the individual to report the suspicious circumstances to the unit executive officer (i.e. head of the department or comparable administrator) of the unit concerned, or to the person appointed annually by the Vice Chancellor for Research as the Officer for Research Standards. The unit executive officers, deans, other administrators involved and the entire academic community, are

charged with protecting the academic careers of persons who have in good faith reported possible fraud or misconduct in scholarship or research.

2. If the person whose conduct is in question is a student, the matter should proceed according to the Code on Campus Affairs and Regulations Applying to All Students, Rule 75.

3. If the person whose conduct is in question is not a student, and if the charges are not obviously frivolous, the unit executive officer or the Officer for Research Standards shall promptly bring them to the attention of the dean or comparable administrator (henceforth referred to as "dean") to whom the executive reports. The dean, in consultation with the Officer for Research Standards, shall appoint an investigative team consisting of one faculty member or academic professional from the unit in which the person whose conduct is in question holds a primary appointment and one faculty member or academic professional from elsewhere within the University to conduct a preliminary investigation as expeditiously as possible. At this time the person whose conduct is in question should be informed in writing of the appointment of the committee and the nature of the allegations.

4. After receiving the report from the preliminary investigative team, the dean shall decide, in consultation with the team and the Officer for Research Standards whether the matter should be dropped or a full investigation should be instituted. If the decision is made not to pursue the case further, all written records should be sealed and deposited in the Office of the Vice Chancellor for Research. Care should be taken that nothing is entered in the personnel file of the person whose conduct had been in question. Both this person and the one who raised the question shall be notified in writing of the decision.

5. If there is sufficient evidence of a serious breach of accepted standards of integrity to warrant further investigation, the person whose conduct is in question and any collaborators in the work concerned shall be informed in writing of the substance of the evidence warranting additional investigation and requested to cooperate with the investigators.

6. A thorough investigation shall be conducted by a committee of three competent scholars, appointed by the dean in consultation with the Officer for Research Standards, and consisting of one staff member from the unit in which the person whose conduct is in question holds a primary appointment, one staff member from elsewhere within the University (they may, but need not be, the same persons who conducted the preliminary investigation) and a peer professional from outside the institution. The person whose conduct is under scrutiny shall be informed in writing of the composition of the committee, and shall be invited to provide the committee with pertinent information.

7. The investigative committee shall, before making its recommendations, provide the person whose conduct is being investigated the opportunity to meet and discuss the case with them with or without counsel. The committee shall then report to the dean. If the committee concludes that no breach of academic integrity has occurred, the case shall be considered closed. If so, all written records shall be disposed of as specified in paragraph 4 of the procedures, and those involved in the case notified in writing of the disposition.

8. If the committee finds substantial evidence of misconduct, the dean shall report the findings to the Chancellor for such further action as is warranted under the Procedures or Statutes of the University.

9. All stages of the investigation up to this point should be treated as entirely confidential. Disclosure of information to anyone not directly involved should be regarded as a serious breach of conduct. At this time, however, the Vice Chancellor for Research should inform such additional individuals as is appropriate in the circumstances. Particularly, funding agencies should be informed unless this has been done earlier because the terms of their funding require it.

APPENDIX E

CONFIDENTIAL

University of Illinois
at Urbana-Champaign

Graduate College
107 Coble Hall
801 South Wright Street
Champaign
Illinois 61820

217 333-0035

December 15, 1983

TO: General University Policy Committee of the Urbana-Champaign Senate

FROM: Theodore L. Brown

SUBJECT: Policy on Academic Fraud and Misconduct

You may recall that more than a year ago I met with the Committee to discuss how we might best proceed toward developing a policy statement regarding academic fraud and misconduct. The result of that meeting was that the General University Policy Committee asked this office to appoint a committee to look into the issues involved, and to generate a draft policy statement. I subsequently appointed such a committee, with the following membership:

Marianne Ferber, Chairperson
Tom Riley, Executive Secretary
David Bantz
Lorella Jones
David Nanney
Eugene Scoles

The Committee has worked diligently to develop a draft policy statement. Once the initial draft was available, the Committee met with several groups on campus to discuss the draft and to receive responses. The groups with whom discussions were held are the following:

Executive Committee of the Graduate College
Research Board
Research Management Advisory Committee
Senate Committee on Academic Freedom and Tenure
Professional Advisory Committee
Faculty Advisory Committee
  Timothy O. Madigan, Legal Counsel, also reviewed the draft

In light of the various comments received from these meetings the Committee redrafted their policy statement and submitted it to this office in November, 1983. Following further discussion of the revised draft with the Executive Committee of the Graduate College, we have made minor modifications to the draft policy submitted by the Committee, and feel it is now ready for more formal consideration. The Faculty Advisory Committee has reviewed the revised draft, and has made very minor suggestions for change. A copy of the revised draft is enclosed.

I should like to emphasize that the intent of the policy statement is to provide for workable, equitable procedures for investigating cases of alleged fraud and misconduct, to the point where the allegations can be dismissed as unfounded, or referred to the Office of the Chancellor for further action on the basis of substantial evidence that fraud or misconduct has occurred. In developing these procedures the Committee has been mindful of policy statements issued at other institutions, and has, as indicated above, received input from a variety of faculty and other groups. Although individuals differ in the details of just how such a procedure should be formulated, we believe that the result of the Committee's work makes very good sense from an academic policy point of view, is practical, and maintains the maximum possible levels of discretion and protection of individual reputations.

I call your attention to one important discovery on the part of the Committee: that the Statutes require rewriting to deal with this particular issue and related issues. As a most obvious example of this need, there is nowhere in the Statutes a provision that such disciplinary cases are to be referred to the Chancellor for action. Rather, the Statutes mandate only that such matters are referred to the President. I feel sure that this language is a leftover from the pre-Chancellor days. In any event, that particular aspect needs to be redone. Further, the Statutes make no provisions for the types of actions that the President or Chancellor can or should take in response to strong indications that a fraud has been perpetrated or that misconduct has occurred. We believe that it will be necessary to develop procedures; however, such development is beyond the scope of the Committee I appointed, and clearly lies within the purview of the Senate's interests.

We hope that this draft will furnish the basis for a campus statement of procedures and policies relating to academic fraud and misconduct. I will be very happy to respond to any comments you might have, or to meet with the committee to discuss the report in more detail.

TLB/aw

Enclosure

cc: K. Andersen, Chairman, Senate Council
H. S. Gutowsky, Chairman, Senate Committee on University Statutes and Senate Procedures
Marianne Ferber
Thomas J. Riley

APPENDIX F (without enclosures)

University of Illinois
at Urbana-Champaign

Institute for Child Behavior and Development
51 E. Gerty Drive
Champaign, IL 61820

CONFIDENTIAL

RECEIVED
MAR 13 1984
GRADUATE COLLEGE

To: Elaine J. Copeland

From: Robert L. Sprague

Date: March 9, 1984

Re: Independence of my data from Steve Breuning's data

In response to your recent request for information about the independence of my experiments and data from that of Steve Breuning's experiments and data, I will address the question by listing a number of points and facts. However, I emphatically state that none of my data has been mixed with, collected by, or contaminated by the experiments and data collection procedures of Steve Breuning.

In one case, Vicky Davis (a friend and companion of Steve Breuning) as an employee of my mental retardation project, collected data on 67 residents of Coldwater Regional Center, Coldwater, Michigan using DIS-Co (Dyskinesia Identification System - Coldwater) between November 8, 1980, and April 2, 1981. In our files, I have copies of the raw data sheets she sent to me, and I have recently reviewed the raw data. The study on Coldwater Center residents was subsequently presented at a convention (New Clinical Drug Evaluation Unit Program, May 1981), but not published. The reason the data was not published was because Vicky Davis had only collected data on 67 subjects while John Kalachnik obtained data on 519 subjects in Minnesota and because the interrater reliabilities were higher in Minnesota. A copy of the published article and attached photocopy of Table 1 which was presented at the meeting only and which shows the Coldwater Center data is enclosed:

1. Sprague, R. L. An analysis of institutionalized retarded residents using DIS-CO, Psychopharmacology Bulletin, 1982, 18 (1), 60-61.

2. To the best of my knowledge, the enclosed list entitled "Cross Search of Stephen E. Breuning and MH 32206" is a complete list of publications arising out of our relationship and funds from grant MH 32206 except these three papers listed below. You will note that none of the 14 papers published by Breuning carries my name.

a. Gualtieri, C. T., Breuning, S. E., Sprague, R. L., & Campbell, M. A centralized data system for studies of tardive dyskinesia (Letter). Journal of the American Academy of Child Psychiatry, 1981, 21, 303-304. This is a letter prepared by C. Thomas Gualtieri about a data system for studying TD (tardive dyskinesia) and contained no empirical data.

b. Sprague, R. L. Litigation, legislation, and regulations regarding psychoactive drug use. In S. E. Breuning & A. D. Poling (Eds.), Drugs and mental retardation. Springfield, IL: Charles C. Thomas, 1982. This is a chapter I wrote for a book edited by Breuning and Poling which contains an extensive review of litigation, laws, and standards of professional organizations and contains no empirical data.

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c. Sprague, R. L., Kalachnik, J. E., Breuning, S. E., Davis, V. J., Ullmann, R. K., Cullari, S., Davidson, N. A., Ferguson, D. G., & Hoffner, B. A. The Dyskinesia Identification System - Coldwater (DIS-Co): A tardive dyskinesia rating scale for the developmentally disabled. Psychopharmacology Bulletin, in press. Originally, the manuscript listed Breuning as a senior author, but since he contributed no empirical data, although he and the others did colaborate in developing the 34 items (Table 1) and definitions (Table 2), I wrote to him recently and said I was changing the order of listing of the authors and revising the manuscript basing the data analysis only on data collected by John Kalachnik as part of our Minnesota TD project. All the data was from Cambridge State Hospital, Cambridge, Minnesota (see Table 4 and page 3).

3. Several people can verify my statements that none of the extensive data from Minnesota have been mixed with, in any way, data from either Coldwater Center or the University of Pittsburgh, the two places Steve Breuning worked during our relationship. It should be pointed out Steve Breuning only worked with mentally retarded people during our relationship, and all of my data on mentally retarded people has come from Minnesota in cooperation with John Kalachnik since the time I met Steve Breuning in 1979 (the first letter to him in my files is dated June 27, 1979).

a. Mr. John E. Kalachnik
Behavior Analyst III
Cambridge State Hospital
Cambridge, MN 55008
phone 612-689-2121, ext 419

John is a graduate of the U of I and has worked at Cambridge State Hospital several years. He has arranged and supervised all the data collected in Minnesota.

b. Mr. Ben F. Wallace
Controller I, Data Processing
Institute for Child Behavior and Development
51 E. Gerty Drive
Champaign, IL 61820
phone 217-333-4123

Ben first started working for the Psychopharmacology Project on June 25, 1979 under CETA funds. Because he is a quite capable data processer, I quickly put him in charge of receiving, filing, and analyzing, under the supervision of graduate students and me, data from our various projects. This responsibility of receiving and filing all our data began about the time I first met Steve Breuning and well before any experiments began at Coldwater Center.

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c. Ms. Rina K. Ullmann
Research Associate
Institute for Child Behavior and Development
51 E. Gerty Drive
Champaign, IL 61820
phone 217-333-4123

Rina has worked with us since May 11, 1976 which is three years before I met Steve Breuning in 1979.

d. Dr. Esther K. Sleator
Institute for Child Behavior and Development
51 E. Gerty Drive
Champaign, IL 61820
phone 217-333-4123

Dr. Sleator has had an appointment with the U of I at the Institute for Child Behavior and Development since September 1, 1972. She has general information about our mental retardation projects, although not specific, detailed information of the other three people because she has primarily worked with hyperactive children.

Sincerely,

Bob

Robert L. Sprague
Director

RLS/sb
Enclosures
cc: D. A. Bernstein
R. L. Linn
M. L. Maehr

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Alcohol, Drug Abuse, and
Mental Health Administration
National Institute of Mental Heal
Rockville MD 20857

January 17, 1984

Dr. Thomas Detre
Associate Senior Vice Chancellor
University of Pittsburgh
221 Western Psychiatric Institute
and Clinic
3815 O'Hara Street
Pittsburgh, Pennsylvania 15213

Dear Dr. Detre:

As you know from our brief telephone conversation, the National Institute of Mental Health (NIMH) has received a letter from the principal investigator on one of its research grants, Dr. Robert L. Sprague, Director, Institute for Child Behavior and Development, University of Illinois at Champaign-Urbana, regarding his concerns about the research of Dr. Stephen E. Breuning, Assistant Professor of Child Psychiatry, Department of Psychiatry, University of Pittsburgh. Dr. Breuning is carrying out research under contract with the University of Illinois that is part of a project supported by this Institute under grant MH-32206, "Use of Psychotropic Drugs with the Retarded;" Dr. Sprague is the principal investigator. In addition, Dr. Breuning is principal investigator on grant MH-37449, "Stimulant Drug Use with Mentally Retarded Children" and has submitted application MH-38184, "Drug/Behavior Therapy in Psychiatrically Ill Retarded" which is currently under review.

Dr. Sprague has expressed concern about unsupportable data reported by Dr. Breuning and has provided two examples as illustration. The first is Dr. Breuning's first progress report on work under his grant MH-37449 (enclosed as appendix 1) which appears to cover work from the period July 1, 1982 to June 30, 1983. (The date 1984 on page 4 of the report appears to Dr. Sprague to be an error.) The following table furnished by Dr. Sprague outlines the number of studies, subjects, sessions, and length of studies reported:

Table 1

Facts on Studies, Number of Subjects, and Length of Studies Reported in MH/HD 37449 Progress Report

Study Number	Subjects	Sessions per Subject	Total Sessions	Length of Study in Days
1	12	4?	48	?
2	11	5?	55	?
3	13	7	91	49
4	24	7	168	49
5	14	9	126	63
6	12	9	108	63
7	13	7	91	49
Totals	99	48	687	273

Dr. Sprague's concern is the unlikelihood of the above studies being conducted in the time period reported. If the report covered only one calendar year, then 261 working days (not subtracting for holidays) were available. Dr. Sprague assumes that the seven reported studies were conducted consecutively because of limitations of subject population and availability of experimental rooms. If that was so, then 273 study days would have been required aside from any additional days needed for the usual delays caused by staff or subject absence, equipment breakdowns, etc.

Second, an abstract is enclosed (as appendix 2) of a paper Dr. Breuning intended to present at the American College of Neuropsychopharmacology last December reporting on a study of 45 subjects followed for two years with six-month assessments. This study has been identified by Dr. Sprague as the continuation of a published study of Gualtieri, Breuning, Schroeder, and Quade, Tardive dyskinesia in mentally retarded children, adolescents, and young adults: North Carolina and Michigan studies, Psychopharmacology Bulletin, 1982, 18, No. 1, 62-65 (enclosed as appendix 3). The Michigan subjects reported on were from the Coldwater Regional Center, Coldwater, Michigan. Dr. Breuning's abstract reports followup on 45 of those subjects for a period of two years. Some of these evaluations appear to have taken place after the date Dr. Sprague understands that Dr. Breuning left Coldwater. While there appears to be some discrepancy in that date as remembered by Dr. Sprague and Dr. Breuning, the Director of the Psychological Services and Behavioral Treatment Program at Coldwater is reported to have no recollection of that data collection. When queried by Dr. Sprague, Dr. Breuning reported that he could locate data on only 24 subjects assessed once at four months and could not locate the subject identification codes.

The allegations we have received are serious and require investigation. Since I understand from my conversations with you and Dr. David Kupfer that the University of Pittsburgh is already investigating this matter and expects the results of that investigation within the next several weeks, we will wait for the results of that investigation before making a decision regarding action by this Institute. We urge that the procedures you have set up follow the guidelines adopted by the American Association of Medical Colleges (enclosed as appendix 4) and that you coordinate your efforts with those of the University of Illinois which is also looking into this matter as it involved Dr. Sprague's work and that University's contract with Dr. Breuning. Dr. T. L. Brown, Vice Chancellor for Research, University of Illinois, is the official with whom you should be in touch.

Although I will be away from my office until February 7, my special assistant, Mr. Michael Moody, will be able to schedule a telephone call with me. His number is (301) 443-6374. As soon as I return, I will be in touch with you about the progress of your investigation.

Sincerely,

Lorraine B. Torres

Lorraine B. Torres
Associate Director for
Extramural Programs

Enclosures

cc: Dr. Breuning
Dr. Sprague
Dr. Brown
bcc: Ms. Jacobs
Mr. Ringler
Mr. Pascal

University of Pittsburgh

WESTERN PSYCHIATRIC INSTITUTE AND CLINIC

January 20, 1984

David Kupfer, M.D.
Professor and Chairman, Department of Psychiatry
University of Pittsburgh School of Medicine
Pittsburgh, PA 15213

Dear Dr. Kupfer:

This letter reports on our meeting of January 16 with Dr. Stephen E. Breuning, and a brief meeting between Drs. Epstein and Breuning on January 18. The first meeting was called in response to your request that we investigate the potential discrepancies in sample size for the follow-up period reported in an abstract, "The course of tardive dyskinesia in the retarded: Longitudinal analysis," submitted by Dr. Breuning to the American College of Neuropsychopharmacology (ACNP) for a panel organized by Dr. Robert Sprague entitled, "Tardive Dyskinesia: Prevalence, Time Course, and Recent Litigation." The panel was initially submitted to ACNP on June 20, 1983, for presentation December 12-16, 1983. The second meeting was held to clarify additional questions about methodology not covered in the first meeting. The purpose of our meetings with Dr. Breuning, as we understood our charge, was to obtain information necessary to resolve the reasons for the sample size discrepancy. In the process of our inquiry we focused on the initial and follow-up data collection that served as the basis for the abstract. We did not attempt to inquire about other research projects conducted by Dr. Breuning.

The meeting reviewed information presented to you by Dr. Breuning on January 6, 1984. The information that was pertinent to our meeting included the following: a summary of the events surrounding this incident by Dr. Breuning, letters exchanged between Dr. Breuning and Dr. Sprague, raw and summary data for subjects in the initial and follow-up study, an abstract presented at the 1981 meetings of ACNP based on the initial 80 weeks of data collection which was published in Psychopharmacology Bulletin, and a paper in press for Psychopharmacology also based on the 80 weeks of the initial study.

The stimulus for this inquiry was the following problem. Dr. Breuning submitted an abstract to Dr. Sprague designed to analyze symptoms of tardive dyskinesia over a 3.5 year period. The data base for this presentation included results for the first 80 weeks which has been previously presented (the initial study), and results collected at week 96 and at six-month intervals beyond week 80 for up to 3.5 years (follow-up).

The subjects were patients at Coldwater State Hospital, where Dr. Breuning worked (through the 96 week assessment) before coming to W.P.I.C. Dr. Sprague became concerned about the existence of the follow-up data, collected after Dr. Breuning had left Coldwater, after a telephone conversation with Dr. Neal Davidson, Director of Psychological Services at Coldwater. Dr. Davidson was unaware of data that was to be collected for this study after Dr. Breuning's move to W.P.I.C. Dr. Sprague thereafter questioned the existence of the follow-up data in a telephone call and letter to Dr. Breuning. When Dr. Sprague requested the follow-up data, Dr. Breuning was able to find raw data for 24 of the 45 subjects in the follow-up sample for week 96, which was the first follow-up interval, but was not able to find any follow-up beyond week 96. In addition, Dr. Breuning was not able to locate any of the raw data for weeks 1 through 80. Based on the inability of Dr. Breuning to produce evidence of the follow-up data, Dr. Sprague requested that Dr. Breuning withdraw the abstract. Dr. Breuning agreed with this recommendation and withdrew the abstract. At the time of our meeting with Dr. Breuning, he had not found the raw data for the initial study or any of the follow-up except for the 24 subjects at week 96.

collection of data by a variety of observers

Based on our discussion it became quite clear that data collected for the initial and follow-up study were not part of a planned protocol. The study was not approved by an IRB, no informed consent was collected for participation in the study, and there was no written protocol for design or data collection. Dr. Breuning reported that during weeks 1 through 96 he and a variety of other staff members collected data on symptoms of tardive dyskinesia in an unsystematic manner, with no attempt to control for time of day, concurrent activity during measurement, social setting, or duration of measurement. No procedures for reliability of measurement were planned, though occasionally the same subject was observed at different times of the day by separate observers.

After considerable discussion during the meeting on this point, Dr. Breuning offered no satisfactory explanation why raw data were available for only 24 of the 45 subjects at week 96 but not for any of the additional follow-up data. Retrospective evaluation of these data, made after Dr. Breuning talked with the person at Coldwater who was responsible for data collection, suggests that they were not collected. It is unclear whether Dr. Breuning was aware that no data had been collected when he wrote the abstract. Dr. Breuning refused to identify the staff member responsible for the data collection. Dr. Breuning reports that on some occasions the data were reported to him by subject number, which provided the opportunity to keep track of the sample size. However, on other occasions the data were reported simply as all subjects were unchanged. Examination of the data sheet used by Dr. Breuning to record these observations did not help to resolve the discrepancies. One final problem in regard to the data collection is that there is no copy of subject names that corresponds to the subject codes. Thus, it is impossible to discern the patients' current level of functioning and impossible to recover any present information about the long-term effects of drug withdrawal.

In addition to the discrepancies in data presentation, there were also problems in the presentation of the research design. The abstract and manuscript present the study as an examination of drug withdrawal in a placebo-controlled, double blind design. However, this design was not actually used. Subjects were withdrawn from medication in either a gradual or an abrupt fashion based on unspecified critieria according to Dr. Breuning's recommendation. Thus, Dr. Breuning both assigned patients to conditions and collected the data, removing any possibility for double blind. The study was also not placebo controlled. After drug withdrawal, patients were provided other pills for an unspecified period of time. The placeboes were selected by the head nurse from an unspecified group of pills, and were used without regard to the size, shape, color, taste, or number of pills presented.

Based on the inability to validate any of the study data, Dr. Breuning reports that a paper in Psychopharmacology has been withdrawn. Dr. Breuning also contacted Natalie Pettich, his project officer at NIMH. It is not clear what he told her, nor is it clear why she was contacted, since his current grants do not appear to be based on the data in question. However, in the Psychopharmacology paper, Dr. Breuning acknowledged that the paper was written in part based on support from grants #MH 30115 given to the Clinical Research Center for Affective Disorders at W.P.I.C.

SB
Objects

In summary, our inquiry suggests that Dr. Breuning did not utilize generally accepted standards for observational methodology and was extremely inaccurate in reporting the research design of the study. In addition, he was extremely negligent in handling and reporting the follow-up data. Our committee did not attempt to establish the motivation for Dr. Breuning's reporting data for 45 subjects during follow-up when the data set was not available.

Respectfully submitted,

104-2247

Leonard H. Epstein

Leonard H. Epstein, Ph.D.
Chairman
Associate Professor of Psychiatry

Michel Hersen, Ph.D.
Professor of Psychiatry

Robert E. Miller

Robert Miller, Ph.D.

Presbyterian-University Hospital of Pittsburgh

DeSoto at O'Hara Streets, Pittsburgh, Pennsylvania 15213
writer's direct dial number:

February 17, 1984

Donald Leon, M.D.
Dean, School of Medicine
M-246 Scaife Hall

Dear Don:

Dr. Breuning is purported to be a leader and a respected investigator in a very active field of psychopharmacology. It is therefore surprising that the series of events that led to the formation of our committee exists.

Our committee met on 3 occasions to study the activities of Dr. Breuning. This included a 2 1/2 hour meeting with Dr. Breuning, phone calls to Dr. R. L. Sprague and C. Thomas Gualtieri and a 1 hour meeting with Dr. Leonard Epstein. Our impressions are in agreement with those of Drs. Epstein, Hersen and Miller as described in their January 20, 1984 letter to Dr. Kupfer. A list of the material we reviewed exists as an appendix to this letter.

The main findings of our committee are:

1. The studies performed at the Coldwater Center in Michigan over a period of 3 1/2 years are unable to be supported by raw data. Neither are these studies supported by any of Dr. Breuning's associates at Coldwater. Dr. R. L. Sprague brought discrepancies in follow-up data to the attention of Dr. Breuning when they were discussing an abstract relating to an upcoming national meeting in early December. Dr. Breuning admitted to us that statements in the abstract were false. Dr. Sprague encouraged Dr. Breuning to withdrew the abstract.

2. Based on the inability to review raw data from the Coldwater study Dr. C. Thomas Gualtieri retracted a paper that was submitted for publication in Psychopharmacology. Dr. Gualtieri was willing to review patient charts in an attempt to substantiate the data but Dr. Breuning told him that this would be impossible since he had no record or recollection of the patients' names.

3. Relating to Dr. Breuning's investigational duties while here in Pittsburgh it should be noted that Dr. Breuning withdrew a NIH grant renewal application 2 days after his initial phone conversation with Dr. Sprague. We are unclear as to the exact reasons for the withdrawal of this grant, but the timing is unfortunate. In addition Dr. Breuning claims that the grant application that was submitted to the NIH was mistakenly an early draft and he provided us with the revised copy that he said should have been submitted. We did not investigate any of Dr. Breuning's work done in Pittsburgh.

Based on the irregularities noted above we feel that it is essential for you to formally investigate Dr. Breuning's research practices.

Sincerely,

Sheldon Adler M.D.

Sheldon Adler, M.D.

Richard Michaels

Richard Michaels, M.D.

Robert E. Lee

Robert E. Lee, M.D., Chairman

REL/deb

List of Materials Reviewed by Drs. Adler, Michaels and Lee

A. Sent to us from the Dean's Office

1. Letter from Dr. Leon forming our committee on 2/3/84 and charging us to investigate apparent discrepancies and irregularities in research conducted by Dr. Stephen Breuning.

2. Research Integrity Policy - University Pittsburgh School of Medicine dated 1983.

3. AAMC Policy on Ethical Standards in Research dated 6/24/82.

4. Copy of abstract entitled: Time Course of Tardive Dyskinesia in the Mentally Retarded: A Longitudinal Analysis by S.E. Breuning labeled appendix 2.

5. Copy of 23 page grant renewal application submitted by Dr. Breuning for an October 1st, 1983 deadline labeled appendix 1.

6. Copy of 4 page article published in Psychopharmacology Bulletin in January, 1982 labeled appendix 3.

7. Copy of letter to Dr. Thomas Detre from Lorraine Torres of the National Institute of Mental Health dated January 17, 1984 describing Dr. Robert Sprague's concerns about Dr. Breuning's research.

8. Copy of report of January 20, 1984 from Drs. Leonard Epstein, Michel Hersen, Robert Miller to Dr. David Kupfer regarding their evaluation of Dr. Breuning's research.

9. Copy of letter from Dr. Kupfer to Dr. Leon dated 1/31/84 reporting the Psychiatry Department's findings.

10. Copy of letter from Dr. Leon to Dr. Breuning dated 1/31/84 notifying him of the appointment of a fact finding committee.

11. Curriculum Vitae of Dr. Stephen E. Breuning dated 1/6/84 provided by Dr. L. Epstein.

B. The following items were given to us by Dr. Stephen Breuning:

1. Copy of letter to Dr. Breuning from Dr. Sprague dated 12/5/83.
2. Copy of letter dated 12/7/83 sent to Dr. Sprague by Dr. Breuning.
3. Copy of letter dated June 14, 1983 sent to but never received by Dr. C. Thomas Gualtieri from Dr. Breuning.
4. Two copies of revised grant renewal applications dated 9/26/83 and 9/28/83.
5. Copy of Dr. Richard Cohen's evaluation of Dr. Breuning dated January 18, 1984 and addressed to Dr. Kupfer.
6. Copy of evaluation of Dr. Breuning's Winter Term 1983 course of graduate students along with a guide to the interpretation of the items rated.
7. Copies of the written survey completed by 13 students who were enrolled in the 395 special education course.
8. Copy of Standard Policies and Procedures for the Coldwater Center dated 7/20/79 and signed by S. E. Breuning and R. L. Rogan.
9. Names and addresses of individuals with whom Dr. Breuning is associated.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Alcohol, Drug Abuse, and
Mental Health Administrat
National Institute of Menta
Rockville MD 20857

May 8, 1984

Donald Leon, M.D.
Dean, School of Medicine
M-246 Scaife Hall
University of Pittsburgh
Pittsburgh, Pennsylvania 15261

Dear Dr. Leon:

Thank you for your letter of March 15 forwarding to me copies of the Department of Psychiatry Preliminary Committee and the Fact Finding Committee reports on allegations concerning Dr. Stephen E. Breuning's research practices. Based upon the information now available to us, we would like to raise the following issues for your consideration.

The January 20th report to Dr. David Kupfer states that the studies carried out by Dr. Breuning at Coldwater Regional Center for Developmental Disabilities, (supported under Grant MH 32206), had no written protocol for design or data collection, had not received approval by an IRB and had not made any provision for obtaining consent either from the subjects or from their legally authorized representatives. If this is true, then violations involving noncompliance with federal regulations governing the protection of human subjects have occurred. Such matters must receive consideration separately from the inquiry into the legitimacy of the research itself inasmuch as the possibilities of harm to human subjects must now be assessed. We have consulted with the Office for Protection from Research Risks at the National Institutes of Health and they have requested us to obtain further documentation, if available, of the evidence which led to the Preliminary Committee's conclusions. Please send that documentation to me. If the evidence warrants, we will pursue the matter further.

In my January 17th letter to you, there were cited two instances of suspicious data which had been reported to us by Dr. Robert Sprague. These were mentioned as examples of what Dr. Sprague suspected might be multiple instances of unsupportable data.

It would appear from the reports you sent me that initial inquiries have focussed exclusively on Dr. Breuning and have been limited to the research he conducted at Coldwater under Grant MH 32206 to the University of Illinois. I am enclosing a copy of a progress report on Grant MH 32206 which reports on the research activities at Coldwater of Ms. Vicky Davis and which also indicates that she was spending ten percent of her time on Dr. Breuning's Grant MH 37449 awarded to the University of Pittsburgh.

We believe that the report of the Research Hearing Board should contain a review of all of Dr. Breuning's federally-supported research activities at the University of Pittsburgh to determine the nature and full extent of any scientific misconduct which may have occurred.

Since there may have been other staff at the University of Pittsburgh who worked with Dr. Breuning on the contract from the University of Illinois under MH 32206 or on Grant MH 37449 to the University of Pittsburgh, we believe that the report should also speak to whether any other staff may have participated in scientific misconduct.

Since Dr. Breuning has resigned from the University of Pittsburgh, we would appreciate your sending us his current address so that we may know his whereabouts during the course of the investigation. We would also like to have information about the current status of Ms. Vicky Davis at the University of Pittsburgh and her address and place of current employment if she is no longer employed there.

In the course of reviewing another application from the University of Pittsburgh, 1 T01 MH 18045-01, NIMH Clinical Training/Human Resource Development, Peter B. Henderson, M.D., we note that Dr. Breuning is listed as one of the participating faculty. This application was neither amended nor withdrawn by the University of Pittsburgh and is scheduled to be reviewed by the National Advisory Mental Health Council on May 21-23. We are therefore requesting the University to review all applications pending with the Public Health Service and to take appropriate action on any on which Dr. Breuning may be included as a participant.

You originally indicated that it would take about six weeks for the Research Hearing Board to complete its investigation. We would very much appreciate current information as to its progress and estimated date for completion of its report.

Please call me if you have any questions. We appreciate your cooperation in this matter.

Sincerely,

Lorraine B. Torres
Associate Director for
Extramural Programs

Enclosure

C. PROGRESS REPORT

1. Dates for period covered by this progress report: September 10, 1979 to April 1, 1981.

This progress report begins with official collaboration between Dr. Robert L. Sprague and Dr. Stephen E. Breuning and ends with the official renewal of the current grant. The renewal is from April 1, 1981 to March 31, 1984. Staff members (all at Illinois), dates and percent of time on project according to year one budget of the current grant (i.e., beginning April 1, 1981) are:

Rina Ullmann, Research Associate	04/01/81 - 08/20/81 09/01/81 - 03/31/82	80% 80%
Vicky J. Davis, Specialist in Child Development	04/01/81 - 04/20/81	75%
Sara Sinclair, Graduate Research Assistant	04/01/81 - 08/20/81 09/01/81 - 03/31/82	50% 50%
Joanne Klitzing, Word Processor Operator III	04/01/81 - 08/20/81 09/01/81 - 03/31/82	80% 80%
Ben Wallace, Data Entry Operator II	04/01/81 - 08/20/81 09/01/81 - 03/31/82	100% 100%

2. Summary of Progress

The research objectives during the period were to: 1) prepare a scale to examine abnormal movements in mentally retarded individuals, 2) to continue development of a resident behavior rating scale with acceptable statistical properties, and 3) examine the effects of withdrawal of psychotropic drugs on the disruptive behaviors for which the drugs were prescribed as well as other measures of adaptive behaviors and performance.

a. Coldwater staff prepared a rating scale to examine dyskinesias in the mentally retarded--Dyskinesia Identification System - Coldwater (DIS-CO). John Kalachnik, a behavior analyst on staff at Cambridge State Hospital in Cambridge, Minnesota, and Vicky J. Davis, Child Development Specialist, assigned to Coldwater Regional Center for Developmental Disabilities, Coldwater, Michigan, trained registered nurses to use the DIS-CO and then supervised the ratings of over 500 residents at Cambridge and 50 residents at Coldwater. Data is currently being analyzed.

b. Coldwater staff revised the Resident Behavior Rating Scale and supervised collection of interrater agreement data. Pairs of raters (ward staff) assessed 21 residents on 10 occasions. Data is currently being analyzed.

c. Vicky J. Davis at Coldwater supervised the gathering of over 60 hours of videotaped dyskinesias and then edited a 9 minute staff training tape. John Kalachnik at Cambridge edited the 60 hours of videotape into a 25 minute training tape and prepared a staff training protocol for the DIS-CO.

MH [illegible] Progress Report 9/01/79 — 9/30/7

Analysis and the Great Lakes Regional Conference of the American Association for Mental Deficiency (copies included).

We have been assured of cooperation from the medical and nursing staff as well as psychologists, educators, other professional staff, and Mr. Robert Rogan, facility administrator at Coldwater Regional Center. Ms. Vicky Davis, project staff member paid by the grant, was formerly a psychologist at Coldwater Regional Center and has excellent rapport with center staff, including LPNs and direct care staff, as well as with residents. She is currently enrolled as a master's degree candidate in behavioral pharmacology at Western Michigan University, supervised by Dr. Alan Poling.

Dr. Breuning is our consultant and liaison at Coldwater Regional Center. He will supervise all research done in conjunction with our project (such as Wysocki's dissertation research) and is our on-site "trouble shooter" should any problems arise requiring immediate attention. Dr. Breuning's value to our project extends far beyond his consultant role, and includes formal, but nonethel vital, contact with members of the administrative and professional staffs, as wel as effective encouragement of qualified personnel to engage in related studies involving drug reduction and withdrawal with chronically-medicated residents. His services to the project are provided by Coldwater Regional Center at no salary cost to the project

Collaboration with University of North Carolina

Dr. C. Thomas Gualtieri is studying tardive dyskinesia in children at the University of North Carolina. He has agreed to use both the Resident Behavior Rating Scale and the Dyskinesia Rating Scale for Developmentally Disabled with his patients in return for our use of AIMS and Withdrawal Emergent Symptoms Checklist with residents at risk of dyskinesia at Coldwater. Dr. Gualtieri has also agreed to serve as psychiatric consultant to Coldwater in the event that a resident appears to be developing dyskinetic symptoms.

Collaboration with Minnesota

We are in the process of arranging data collection on the extent of dyskines at two institutions for developmentally disabled individuals in Minnesota. Preliminary meetings at Cambridge State Hospital and Brainerd State Hospital have indicated a strong interest of administrators and medical directors at both facilities in examining the incidence of dyskinesia among the residents. Moreover, one of my former students, Mr. John Kalachnik, is presently on the staff at Cambridge State Hospital and has agreed to coordinate these efforts with the concurrence of the facility. Cambridge State and Brainerd State have agreed to provide personnel to complete the ratings, in exchange for rating scales, training and data analysis to be supplied by our staff. In addition, Cambridge State has indicated the possibility of obtaining videotape records of residents showing abnormal movements. These tapes would be used to compare coding standards at Cambridge with those at other collaborating institutions.

3. Goals for next year

Our first goal is to complete the Dyskinesia Rating Scale for Developmentall Disabled, assess its stability over time, and make it available for workers in the area.

University of Pittsburgh
SCHOOL OF MEDICINE
Office of the Dean

CONFIDENTIAL

July 6, 1984

Ms. Lorraine B. Torres
Associate Director for
Extramural Programs
Department of Health and
Human Services
National Institute of
Mental Health
Rockville, MD 20357

Dear Ms. Torres:

I am pleased to forward you copies of minutes of our internal hearing board which was appointed to review and report on Dr. Stephen Breuning.

They report that there is no evidence that any of the grant activity (MH37449) was conducted without appropriate IRB approvals, and that there is no evidence of direct relationships between his studies at Coldwater and those here in Pittsburgh at Western Pennsylvania Psychiatric Institute and Clinic (University of Pittsburgh). Briefly stated, our Hearing Board can find no serious fault with Dr. Breuning's activities here in Pittsburgh.

Leonard Epstein, Ph.D. in his letter to Dr. David Kupfer of January 20, 1984 makes reference on page two to the absence of IRB approval of studies at Coldwater. This letter is the report of the departmental review committee which is required in our procedures.

Dr. Epstein has reported to me that Dr. Breuning had stated that there had been no IRB approval, in fact, that there was no IRB at Coldwater. Breuning's explanation for this was that Coldwater was a state institution and that patients on admission signed some sort of consent to be observed or studied. Worse than this, there was no protocol for the "study", it was rather a series of "random" observations collected by various observers and not in a controlled study fashion. In fact, it was not a "placibo double blind" study at all.

Our Hearing Board has sent a brief final report, a copy of which is enclosed. Based on this report and that fact that Breuning has left the University of Pittsburgh, I have no grounds to take action against him relative to his activities while a member of our faculty.

Sincerely,

Donald F. Leon, M.D.

DFL:lmf

Enclosure

cc: Thomas Detre, M.D.
David J. Kupfer, M.D.
Mr. Ronald Talarico

University of Pittsburgh
SCHOOL OF MEDICINE
Department of Biochemistry

RECEIVE
JUL 06 1984
DEAN, SCHOOL OF MEDIC

CONFIDENTIAL

July 5, 1984

Donald F. Leon, M.D.
M-246 Scaife Hall

Dear Don:

The purpose of this letter is to report the findings of the Research Hearing Board appointed by you to investigate apparent discrepencies and irregularities in the research conducted by Dr. Steven Breuning. Since Dr. Breuning has resigned from the University of Pittsburgh, the scope of the hearing board was limited to determine if the research in question resulted in misuse of NIMH funds.

The members of the committee individually reviewed all materials previously collected and then met on May 3, 1984 to discuss this evidence and to further question Dr. Breuning. The minutes of that meeting are attached. As a result of this review and of further information received from Dr. Kupfer (enclosed), the committee has unanimously concluded that the follow up studies that were reported to have been carried out at Coldwater were not used as a basis for application or receipt of funds from NIMH. In addition, as best we can determine, the work in question did not significantly effect the conduct of other research carried out by Dr. Breuning at the University of Pittsburgh or the expenditure of grant support which he received from NIMH. Thus, the committee has concluded that no misuse of funds occurred and that this matter should be closed.

Sincerely yours,

Norman P. Curthoys, Ph.D.
Professor and Chairman

cc: Members of Hearing Board
Dr. S. Breuning

Minutes of Hearing Board Meeting
May 3, 1984

The Medical School Research Hearing Board appointed to investigate apparent discrepencies and irregularities in the research conducted by Dr. Stephen Breuning met at 7:00 a.m. on Thursday, May 3, 1984. Present at the meeting were Drs. Bahnson, Curthoys, Gill and Rosenberg, Mr. Ronald Talerico, Esq., Dr. Stephen Breuning and his counsel, Mr. Thomas Coval, Esq. Individuals invited to present testimony to the Hearing Board included Dr. David Kupfer, Chairman of Psychiatry, Dr. Sheldon Adler, member of the Dean's fact finding review panel, and Dr. Leonard Epstein, Chairman of the preliminary review committee appointed by Dr. Kupfer.

The meeting was opened by Dr. Curthoys who reviewed the charge given to the Hearing Board by the Dean and the previous steps in the review process which led to the appointment of this Hearing Board. Since Dr. Breuning has resigned his position at the University of Pittsburgh effective April 30, 1984, the remaining purpose of the Hearing Board is to determine if the research in question was used as a basis for application, receipt or expenditure of grant support from NIMH. Potential grants in question include the subcontract of NIMH grant 32206 dealing with psychotropic drugs that was awarded to Dr. Robert Sprague for the period of May 1981 through April 1984 and NIMH grant 37449 dealing with the use of stimulant drugs awarded to Dr. Stephen Breuning, for the period of July 1981 through June 1984. The latter grant has been terminated and as a result, neither grant is currently in effect.

In opening statements, Mr. Coval pointed out that the sole research in question was the collection and validity of follow-up data for the Coldwater studies that were conducted after Dr. Breuning had arrived at the University of Pittsburgh in January 1981. None of the studies conducted at Coldwater were sponsored by an NIMH grant. In addition, the follow-up studies were carried out after the two grants in question were submitted to NIMH for review. Thus, the follow-up studies conducted at Coldwater were not included in either application. The committee then decided to determine to what extent the research in question influenced subsequent studies conducted by Dr. Breuning under the sponsorship of NIMH. Mr. Coval indicated that the presence of Dr. Breuning at this hearing did not imply recognition of the jurisdiction of the appointed Hearing Board.

Dr. Kupfer then reviewed the initial events which led to his decision to appoint a fact-finding committee to review the credibility of data collected in the follow-up studies at Coldwater. Dr. Breuning indicated that none of the studies carried out at Coldwater were sponsored through a formal subcontract of an NIMH grant. Such support occurred only after moving to the University of Pittsburgh and that these funds were used to carry out studies that were different from those initiated and conducted at Coldwater. Dr. Kupfer indicated that the Hearing Board would need to review this question more carefully but to the best of his knowledge, the only reference to the data in question was the abstract to be presented at the ACNP meeting which was withdrawn by Dr. Breuning and the Psychopharmacology paper submitted and then later withdrawn by Dr. Gualtieri. Dr. Breuning then stated that the follow-up data from Coldwater had not been presented anywhere or in any publication. That it was not used as a basis for any grant application and that the announcement of the conference proceedings that appeared in the Psychopharmacology Bulletin gave reference only to the original study.

Dr. Adler then reviewed for the Hearing Board the results of the fact-finding panel that are presented in the letter of Dr. Lee dated February 27, 1984. Dr. Alder indicated that the results of their review raised sufficient questions that they recommended further inquiry into the research conducted by Dr. Breuning. In response to questions from Mr. Coval, Dr. Adler indicated that the committee had not examined whether the data in question was used as the basis of a grant application or of further studies conducted using support from NIMH. Dr. Epstein then summarized the findings of the initial review committee which are contained in the letter dated January 1, 1984.

Immediately following the collection of testimony, the Hearing Board met in executive session and decided to limit further investigation to the question of whether the follow-up studies carried out after Dr. Breuning left Coldwater influenced the conduct of Dr. Breuning's sponsored research at the University of Pittsburgh, and in what way did funds from the NIMH Clinical Research Center Grant awarded to the Department of Psychiatry contribute to the reporting, presentation or continuation of any of the follow-up studies carried out at Coldwater. Dr. Kupfer was requested to collect this information by appointing an appropriate committee to review Dr. Breuning's grant applications and publications to determine the answers to these questions.

The meeting was adjourned at 9:05 a.m.

University of Pittsburgh

SCHOOL OF MEDICINE DEPARTMENT OF PSYCHIATRY
Office of the Chairman

May 31, 1984

Norman P. Curthoys, Ph.D.
Professor and Chairman
Department of Biochemistry
University of Pittsburgh
School of Medicine
814, Scaife Hall

Dear Norman,

I am writing to you in your capacity as Chairman of the Medical School Research Hearing Board investigating the activities of Dr. Stephen Breuning. When I testified before the committee, I was asked by you to obtain further information concerning two specific issues. First, whether any of the research activity performed by Dr. Breuning during his tenure at the University of Pittsburgh and carried out at the University of Pittsburgh was performed without the appropriate IRB approvals. Furthermore, whether any of the research activity at Coldwater was conducted by Dr. Breuning under the auspices of University of Pittsburgh approved protocols. Secondly, I was asked to obtain information concerning the use of data from the Coldwater studies in the research conducted by Dr. Breuning at WPIC.

We have examined these issues and have concluded the following:

1. There is no evidence that any of the grant activity (MH 37449) was conducted without the appropriate IRB approvals.

2. However, certain of the procedures used in Dr. Breuning's studies at WPIC initially had been developed and tested in his earlier work, much if not all of which was done at Coldwater.

3. On his arrival at WPIC, Dr. Breuning continued to pursue those research interests he had earlier developed, specifically drug efficacy studies for the treatment of mentally retarded children. Therefore, it is not surprising that his prior investigatory work at Coldwater influenced his choice of problem areas here, as well as his research designs and experimental methodology. This is most clearly seen in the subcontract work that he did with Dr. Robert Sprague, which apparently was arranged very shortly after Dr. Breuning's arrival in Pittsburgh and represented a kind of continuation of their prior collaboration.

4. Dr. Breuning's studies of stimulant drugs at WPIC seem less directly influenced by his Coldwater work, although the design and procedures used surely were similar to what he had used earlier. Here too, however, there is no direct evidence that any of the Coldwater data were utilized. Nonetheless, there was a kind of continuity from Breuning's earlier studies on neuroleptics to his later work on stimulant drugs.

Therefore, there does not appear to be any direct relationship between the Coldwater activities and Dr. Breuning's research activities at WPIC.

Sincerely yours,

David

David J. Kupfer, M.D.

DJK:gmd

University of Pittsburgh

WESTERN PSYCHIATRIC INSTITUTE AND CLINIC

CONFIDENTIAL

MEMO TO: DAVID KUPFER, M.D.
CHAIRMAN, DEPARTMENT OF PSYCHIATRY

FROM: THE AD HOC INVESTIGATING COMMITTEE

DATE: MAY 3, 1985

TOPIC: FINAL REPORT OF THE AD HOC COMMITTEE

HISTORY: On March 14, 1985 Dr. Kupfer appointed an Ad Hoc committee consisting of Drs. Robert Miller (Chairman), Nancy Day, Leonard Epstein, and Karen Matthews to investigate the record of research conducted by Dr. Steven Breuning at WPIC. Specifically, the committee was charged to determine the authenticity of the data reported in the 01 progress report of research grant MH37449, "Stimulant Drug Use with Mentally Retarded Children." It was also decided to expand the investigation to include the seven studies reported in the Previous Work section of the renewal application submitted to NIMH on October 1, 1983 under the same title. The renewal was subsequently withdrawn by Dr. Breuning before it underwent review but the seven studies listed had purportedly been completed during the support period of 7/1/82 to 6/30/84 of MH37449.

Inspection of the 01 Progress Report and the Previous Work section of the renewal application for MH37449 indicated that data from a total of 99 retarded subjects given stimulant trials were reported. Table 1 summarizes the number of subjects and the experimental conditions for each of the seven studies listed in the renewal application.

PROCEDURES: After each of the committee members had an opportunity to examine the materials provided to the committee, two meetings were held to establish procedures to obtain the requisite data concerning the charge to verify the research data reported in the Progress Report and the renewal application. The committee followed the procedures outlined below:

1. The members of the committee personally searched the individual medical records of all 278 inpatients admitted to the Merck Unit between July 1, 1980 and June 30, 1984. The search included: inspection of the daily orders from physicians; inspection of the medications record; and examination of the Discharge Summary. If evidence of any administration of either Ritalin or Dexadrine was found, a separate data sheet was prepared and the record was carefully examined in detail to check for IRB consent, evidence of behavioral testing in the daily progress notes, and the specific discharge diagnosis.

2. Copies of all placebo-controlled trials conducted on the Merck Unit from 1980-1984 were obtained from the WPIC pharmacy to establish which patients had received stimulant/placebo double-blind studies.

3. The Chairman interviewed Dr. Patrick Ackles by phone on March 24, 1985. Dr. Ackles had been a Post-Doctoral Fellow working directly with Dr. Breuning on the John Merck Unit during the period of 7/1/83 to 6/30/84. It was thought that Dr. Ackles would have direct knowledge of the research activities on the Unit at that time.

4. On April 1, 1985 the Chairman interviewed Dr. Alan Poling of Western Michigan University by phone. Dr. Poling was senior author on a paper with Dr. Breuning, "Effects of methylphenidate on the fixed-ratio performance of mentally retarded children", Pharmacology, Biochemistry and Behavior 18: 541-544, 1983 and a co-author with Drs. Breuning and Ackles on a second paper, "Dose-dependent effects of methylphenidate on the fixed-ratio performance of hyperactive severely retarded adolescents" in press in Applied Research in Mental Retardation. Both of these papers had been cited in the Progress Report section of the renewal application.

5. Lori Sisson, the Project Coordinator on MH37449, was interviewed on April 4, 1985 to discuss her knowledge of the research activities on the Merck Unit.

6. The Committee interviewed Edward Nuffield, M.D., Medical Director of the Merck Unit during the relevant time period, on May 1, 1985 and Janice Forster, M.D., a staff physician on the Unit, on April 26, 1985. The purpose of these interviews was to ascertain the procedures which were employed to assign a patient to the research protocol on stimulant drugs, procedures for obtaining informed consent from parents, and methods for conducting the double-blind drug protocols.

7. The Chairman obtained copies of the relevant IRB renewal reports from the Secretary of the IRB (Biomedical) of the University of Pittsburgh.

RESULTS: Each of the sources of information provided useful evidence to the Ad Hoc committee with regard to the research studies conducted on the Merck Unit during the period 7/1/82 to 6/30/84. This report will place the highest weight on the written documentation from medical and pharmacy records. The information obtained from interviews supplements the written record and supplies valuable insights into the process of the conduct of the research but is, of course, subject to the errors of specific recall of events that occurred many months ago.

1. Inspection of Medical Records and Pharmacy Orders.

An exhaustive search of the Medical Records of 278 admissions to the John Merck Unit from July 1, 1980 to June 30, 1984 disclosed that 25 patients had ever received either Ritalin or Dexadrine while a patient on the Unit. The disposition of these cases is as follows:

a. Eight subjects had received either Ritalin or Dexadrine as a prescribed medication for a brief period of time but without placebo control or, in many instances, any behavioral testing on the matching-to-sample procedure (MTS). In some cases, the stimulant was being withdrawn over the first few days of admission or was given as a test dose for only a day or two. These eight patients, therefore, do not qualify as research subjects for the stimulant grant.

1984 when Dr. Breuning was no longer a member of the Department. Further, neither of these patients had an IRB consent in their medical record nor was there any evidence in progress notes that they had received MTS testing.

c. Of the remaining 15 patients who had received stimulant/placebo trials, four had no evidence in daily progress notes of MTS testing. Since such testing was always recorded in the notes, these four patients do not appear to have been research subjects.

d. There were 11 patients who received stimulant/placebo trials *and* MTS testing. Only *two* of these subjects had IRB informed consents in the medical record. Pharmacy records confirmed that these 11 subjects had been administered stimulant and placebo according to a double-blind procedure. In the absence of documented informed consent, it was not possible to discriminate among subjects who were being tested clinically for the effects of stimulants and those who were entered into the research protocol.

A detailed examination of the 11 patients who could have been research subjects disclosed a number of deviations from the procedures which had been outlined in grant #MH37449:

(1) The original protocol specified that subjects would have a diagnosis of Attention Deficit Disorder with Hyperactivity and Mild Mental Retardation. Only 4 of the 11 patients on stimulant/placebo trials had a discharge diagnosis that met these criteria.

(2) The protocol specified that MTS testing would be done in a tightly scheduled manner within 90-120 minutes after the 8:00 AM administration of the drug. Data in the medical records revealed that the timing of the laboratory testing was rarely within the prescribed time limits and, in fact, often varied widely within the same subject over testing days.

(3) While the protocol states that the stimulant will be administered once daily at 8:00 AM, the pharmacy records indicate that divided doses at 8:00 and 12:00 were sometimes used.

(4) According to the protocol, children aged 3-6 would be given dextroamphetamine trials while those 6-12 would receive Ritalin. Two of the subjects on Dexadrine/placebo trials exceeded the stated age range (8 years and 11 years of age). The four subjects given Ritalin were all within the precribed age range.

2. Telephone interview with Dr. Patrick Ackles.

Dr. Ackles, who is currently working in Chicago, was interviewed by the committee Chairman by phone. He was most cooperative in responding to questions about the research conducted during his Fellowship on the Merck Unit. He stated that his involvement on the paper accepted by *Applied Research in Mental Retardation* with Drs. Breuning and Poling was limited solely to some statistical analyses and preparation of graphs from summary data sheets given to him by Dr. Breuning. He said that Dr. Breuning first told him that the data were collected at WPIC but, when Dr. Ackles pointed out that the ages of subjects did not match that of Merck Unit patients, Dr. Breuning stated that the data were obtained elsewhere.

Dr. Ackles said that, to his knowledge, no subjects were ever tested in Pittsburgh on a fixed-ratio regimen. The apparatus was on the unit but was never connected-up or operational.

3. Telephone interview with Dr. Alan Poling.

Dr. Poling denied any direct knowledge of the fixed-ratio testing of the 23 subjects reported in the two papers which he co-authored with Dr. Breuning. He stated that he was given summary data sheets by Dr. Breuning from which the reports were prepared but that he did not participate in any direct data collection. He was under the impression that these data had been collected from subjects in Pittsburgh but could not be sure.

4. Interview with Lori Sisson.

Drs. Robert Miller and Nancy Day met with Lori Sisson, Research Coordinator, on April 4, 1985. It had been Ms. Sisson's job to schedule and supervise the matching-to-sample (MTS) procedures, to prepare daily graphs of the data, and to coordinate all research activities connected with the stimulant grant.

Ms. Sisson was most cooperative throughout the interview, even bringing along her testing schedules for examination by the committee. Since she was blind regarding medication regimens and, therefore, did not attend the planning conferences, she could not specify which of the patients had been on stimulant trials. She did assert that it was the practice on the Unit to place patients on the MTS procedure irrespective of their participation in a research protocol.

In the course of the interview, several salient points emerged:

a. No fixed-ratio testing was ever done on the Merck Unit.

b. No testing was ever conducted on patients from other units at WPIC or on outpatients. All of the relevant data for the stimulant grant should have been collected from inpatients on the sixth floor.

c. Ms. Sisson was seldom given instructions to test patients within specific time-frames to correspond with the "therapeutic window" for drug effects which is outlined in MH37449.

d. The data which Ms. Sisson plotted from the MTS testing of subjects on the Merck Unit were, without exception, essentially flat curves. When Dr. Breuning showed her graphs of data showing dramatic drug effects, she questioned their source since her data did not reflect such effects. Dr. Breuning replied that he was working in collaboration with a number of investigators around the country and they had produced these data. He did not identify those sites or investigators.

TABLE 1

Stephen E. Breuning
Grant: Stimulant Drug Use with Mentally Retarded Children
Review of Previous Research 7/1/82 - 9/1/84

Authors	S	Drug/Doses	Behavior
1. Poling & Breuning	12	Methylphenidate P,.3,.7,1.0	FR 5,10,20
2. Breuning, Ackles, & Poling	11 15-18	Methylphenidate P,.3,.5,.7,1.0	FR 5,10,20
3. Breuning, Sisson, Ackles, Nuffield, Phillips, & Barrett	13 14-18 8M,5F	Methylphenidate P,.3,.7,1.0 7d/phase P,D1,P,D2,P,D3,P	FR 5,10,20
4. Breuning, Sisson, Davis, Ackles, Fultz, Duffner, Forster, & Barrett	24 6-12 17M,7F	Methylphenidate .3,.5,.7 7d/phase P,D1,P,D2,P,D3,P	MTS
5. Davis, Breuning	14 Mean=8.95 9M,5F	Methylphenidate .3,.5,.7,1.0 7d/phase P,D1,P,D2,P,D3,P,D4,P	MTS
6. Ackles & Breuning	12 Mean=4.61 9M,3F	Dextroamphetamine .15,.25,.35 7d/phase P,D1,P,D2,P,D3,P	MTS
7. Breuning, Ackles, Sisson, Fultz, Camparo, Forster, Nuffield, & Barrett	13 Mean=4.7 9M,4F	Dextroamphetamine .15,.25,.35 7d/phase P,D1,P,D2,P,D3,P	MTS

APPENDIX C
STEPHEN E. BREUNING BIOGRAPHICAL MATERIAL

13

Date Revised: 1-6-84

BIOGRAPHICAL

Name	Stephen E. Breuning
Birthdate	9/18/52
Birthplace	Mineral Wells, Texas
Citizenship	U.S.
Social Security #	381-56-6478
Business Address	Department of Psychiatry Western Psychiatric Institute & Clinic University of Pittsburgh School of Medicine 3811 O'Hara Street Pittsburgh, PA 15213
Home Address	12 Bethany Drive Pittsburgh, PA 15215
Telephone (Work)	412-624-2331
Telephone (Home)	412-784-1760

EDUCATION AND TRAINING

Undergraduate

9-70 to 8-73	Western Michigan University Kalamazoo, Michigan	B.S., 1973	Psychology, Biology
8-73 to 8-74	Western Michigan University Kalamazoo, Michigan	M.A., 1974	Dr. Howard E. Farris, Psychology
9-74 to 5-77	Illinois Institute of Technology	Ph.D., 1977	Dr. Allen H. Wolach, Psychology

APPOINTMENTS AND POSITIONS

Academic

9-76 to 9-77	Trinity Christian College Palos Hills, Illinois	Instructor
9-79 to 8-83	Western Michigan University	Adjunct Assistant Professor, Department of Psychology
1-81 to present	Western Psychiatric Institute & Clinic University of Pittsburgh School of Medicine Pittsburgh, Pennsylvania	Assistant Professor of Child Psychiatry

6-81 to present	Western Psychiatric Institute & Clinic University of Pittsburgh School of Medicine Pittsburgh, Pennsylvania	Acting Director/Research Director John Merck Program for Multiply Disabled Children

Non-Academic

4-72 to 12-72	Kalamazoo Regional Psychiatric Hospital Kalamazoo, Michigan	Research Assistant
1-72 to 7-73	Kalamazoo Valley Multihandicap Center Kalamazoo, Michigan	Behavior Analyst
1-72 to 7-73	Student Centered Education Project Kalamazoo, Michigan	Educational Technologist
9-75 to 5-77	Illinois Institute of Technology Chicago, Illinois	Teaching Assistant
3-76 to 12-77	South Suburban Chicago Schools Project Chicago, Illinois	Director of Behavioral Programs and Research
-77 to 9-78	Oakdale Regional Center for Developmental Disabilities Lapeer, Michigan	Psychologist
9-78 to 1-81	Coldwater Regional Center for Developmental Disabilities Coldwater, Michigan	Psychologist, Research Director

CERTIFICATION AND LICENSURE

Licensed Clinical/Consulting Psychologist (#003205) by the Michigan Department of Licensing and Regulations

MEMBERSHIP IN PROFESSIONAL AND SCIENTIFIC SOCIETIES

1975 to 1979	Association for Behavior Analysis
1977 to present	American Association on Mental Deficiency
1982 to present	Association for the Advancement of Behavior Therapy

HONORS

1973	Graduated Cum Laude
1974	Graduated with Honors
1979-1981	Chairperson, Mental Retardation Division, Association for Behavior Analysis.
1982-1983	Chairperson, Psychology Division, Region IX, American Association on Mental Deficiency.
1983-1984	Second Vice-Chairperson, Pennsylvania Chapter, American Association on Mental Deficiency.
1983-1984	First Vice-Chairperson, Pennsylvania Chapter, American Association on Mental Deficiency
1983-1984	Member, Controversial Treatments Review Section, Professional Consulting Services and Peer Review Committee of the Association for the Advancement of Behavior Therapy.
1983 -	Tardive Dyskinesia Litigation Professional Advisory Committee, Developed at the Pharmacological and Somatic Treatments Research Branch of NIMH Workshop entitled "Tardive Dyskinesia in the Developmentally Disabled".

SEMINARS ON

BEHAVIORAL MEDICATION ISSUES

MAY 10 — 1:30 - 3:30 McDOUGALL TRAINING CENTER

"METHODOLOGICAL CONSIDERATIONS IN USING OBSERVATIONAL DATA FOR CLINICAL DECISIONS"

DR. TED RUGGLES Ph.D.
SONOMA DEVELOPMENTAL CENTER

MAY 17 — 1:30 - 3:30 McDOUGALL TRAINING CENTER

"INVOLUNTARY MOVEMENT DISORDERS: PREVELANCE AND DISORDERS"

DR. RON STONE AND BARBARA FEDULLO, R.N.
SONOMA DEVELOPMENTAL CENTER

MAY 24 — 8:30 - 5:00 VETERANS AUDITORIUM, SONOMA

"MAKING INFORMED DECISIONS: BEHAVIORAL MEDICATIONS"

DR. STEVEN BREUNING Ph.D.
UNIVERSITY OF PITTSBURGH — SCHOOL OF MEDICINE

TOM COVAL, ATTORNEY
TEMPLE UNIVERSITY — WOODHAVEN SCHOOL, PENNSYLVANIA

DR. LEONARD FIELDING — DIRECTOR
BRAINARD REGIONAL HUMAN RESOURCES CENTER, MINN.

DR. JOE TOUPIN — MEDICAL DIRECTOR
U.C. DAVIS SCHOOL OF MEDICINE

THIS TRAINING EVENT IS SPECIFIC TO THE BEHAVIORAL, MEDICAL AND LEGAL DECISIONS ASSOCIATED WITH CONTINUED USE OF PSYCHTROPIC MEDICATIONS.

- 7 CEU'S AVAILABLE FOR RN'S AND LVN'S

CRISIS IN MENTAL RETARDATION

Legal and Treatment Implications of ?harmacological and Behavioral Interventions

Albany, New York
May 19-20

WORKSHOP DESCRIPTION

No longer is treatment of the mentally retarded a moral or ethical issue. With increasing frequency, the judicial system is determining that EFFECTIVE (not just benign) treatment is a legal right of the classified retarded. As psychotropic medication has increased with de-institutionalization, so has the documented incidence of psychological and physical disorders. This is no longer deemed tolerable, and individuals, from the ward attendant to the institutional director, are being held personally liable for poor treatments.

What exactly is our legal responsibility? What exactly comprises good and effective treatment?

This eminent team of trainers is well-known in the U.S. for being in the forefront of this movement. They have been working extensively with institutions and Federal and State officials at reconceptualizing treatment approaches to best meet the needs of retarded citizens. Their presentation is dynamic and pragmatic. Participants will learn of specific court cases, legal treatment requirements and a team-oriented working approach to treatment.

TARGETED AUDIENCE AND LEVEL

Administrators and treatment team members, advocates and particularly affiliated medical personnel will find this conference challenging and useful. Some knowledge of usual treatment strategies is necessary for meaningful participation.

'E PRESENTERS

hen E. Breuning, Ph.D., is . administrator of Medical, Nursing and Psychological Services at the Polk Center for the Mentally Retarded in Pittsburgh, Pennsylvania. Prior to his position at Polk Center, he spent three years as assistant professor of psychiatry and director of services for developmentally disabled children at the University of Pittsburgh Western Psychiatric Institute and Clinic. He has published six books and numerous journal articles in the areas of mental retardation and psychopharmacology and behavior modification. Breuning is currently regarded as one of the nation's top treatment experts in the field of Mental Retardation.

Thomas E. Coval, Esq., is a trial lawyer in private practice in Philadelphia, Pennsylvania and is legal counsel to Temple University Medical Center for the Developmentally Disabled. He specializes in legal work pertaining to behavioral and pharmacological treatment of the mentally retarded. He has authored several articles in legal journals on the topic of his specialty; and is quite well known for his expertise in legal matters related to classified retarded.

Vicky J. Davis, M.A., is Educational Specialist at the Polk Center. She has written several publications in the areas of mental retardation, clinical assessment and psychopharma- gy, and is known for her with staff training for effec- treatment.

SCHEDULE

MONDAY, MAY 19, 1986

8-9 a.m.	Registration & Coffee
9-10 a.m.	Orientation: a survey of research, issues and applications
10-10:15 a.m.	BREAK: Coffee, tea, and pastries.
10:15 a.m.-Noon	A comprehensive approach to assessment and treatment of behaviorally disturbed retarded clients
Noon-1 p.m.	LUNCHEON
1-2:30 p.m.	Legal and administrative aspects of behavioral and pharmacological treatments.
2:30-2:45 p.m.	BREAK: soda and fruits
2:45-5 p.m.	The mental health professional as expert witness: simulations of actual court cases.
9-10:30 p.m.	RECEPTION: cash bar and hors d'oeuvres

TUESDAY, May 20, 1986

9-10:15 a.m.	Questions you *will* be asked by attorneys, and suggested answers you should have.
10:15-10:30 a.m.	BREAK: coffee, tea and pastries.
10:30-Noon	Client informed consent: current legal and ethical requirements for obtaining treatment with pharmacological and psychological interventions.
Noon-1 p.m.	LUNCHEON
1-2:30 p.m.	Discussion of recent cases and practical implications
2:30-2:45 p.m.	BREAK: soda and fruits
2:45-4:30 p.m.	Question and answer forum. Participants are asked to prepare questions in advance and give them to the conference directors.
4:30-5 p.m.	Continuing Education and Academic Credits. Participants wishing credit will fill out forms and take post-tests to evaluate our training conference.

ASSESSMENT AND TREATMENT OF ANXIETY AND PHOBIC DISORDERS

Syracuse, New York
June 16-17, 1986

WORKSHOP DESCRIPTION

This workshop is designed to provide clinicians with a working knowledge of the classification and treatment of: Agoraphobia, Panic Disorder, Generalized Anxiety Disorder, and Obsessive-Compulsive Disorder. Insofar as treatment is linked to diagnostic classification, Dr. Barlow will give special attention to distinguishing the various anxiety disorders to help practitioners deliver specialized treatment regimens.

The information presented is grounded in well controlled scientific experimentation. However, it should also be stressed that Dr. Barlow is an accomplished clinician having himself treated many of the cases he will discuss. Dr. Barlow's knowledge of these disturbances emanates not only from his clinical encounters, but also from ongoing research projects at the Center for Stress and Anxiety Disorders and the Phobia and Anxiety Disorders Clinic at SUNY Albany. These projects have yielded scientifically grounded data which clinicians may utilize in a more systematic fashion than that knowledge gained only through anecdotal reports of treatment.

The assessment and treatment of anxiety and phobic disorders are considered by many practitioners to be topics of preeminent concern. Our own needs assessment surveys and a recent article in the APA Monitor support this conclusion. It would certainly behoove the therapist who wishes to stay current in this important field to attend Dr. Barlow's workshop.

TARGETED AUDIENCE AND LEVEL

Psychiatrists, psychologists, social workers and allied health professionals, along with graduate students in those professions.

THE PRESENTER

David H. Barlow received his Ph.D. from the University of Vermont in 1969 and has published over 150 articles and chapters and seven books, mostly in the areas of anxiety disorders, sexual problems, and clinical research methodology. His most recent books include: Mavissakalian, M., and Barlow, D.H., **Phobia: Psychological and Pharmacological Treatment.** New York: Guilford Press, 1981; Barlow, D.H., and Hersen, M. **Single Case Experimental Designs: Strategies for Studying Behavioral Change, 2nd Edition.** New York: Pergamon, in press; Barlow, D.H. (ED.), **Clinical Handbook of Psychological Disorders: A Step-By-Step Treatment Manual.** New York: Guilford Press, 1985.

Dr. Barlow is a professor in the Department of Psychology at the State University of New York at Albany. He is Past President of the Association for Advancement of Behavior Therapy, and Associate Editor of several journals. At present he is co-director of the Center for Stress and Anxiety Disorders and also director of the Phobia and Anxiety Disorders Clinic and the Sexuality Research Program at SUNY Albany. He is a Diplomate in Clinical Psychology of the American Board of Professional Psychology and maintains a private practice.

SCHEDULE

MONDAY, JUNE 16, 1986

9-10:30 a.m.	Phenomenology and Classification of Anxiety Disorders
10:30-11 a.m.	BREAK
11 a.m.-Noon	Phenomenology and Classification of Anxiety Disorders
Noon-1 p.m.	LUNCH
1-2:30 p.m.	Assessment and Treatment of Panic Disorder, Agoraphobia, and Generalized Anxiety Disorder
2:30-3 p.m.	BREAK
3-4:30 p.m.	Assessment and Treatment of Panic Disorder, Agoraphobia, and Generalized Anxiety Disorder
4:30 p.m.	Cocktail Party (Cash Bar)

TUESDAY, JUNE 17, 1986

9-10:30 a.m.	Assessment and Treatment of Panic Disorder, Agoraphobia, and Generalized Anxiety Disorder
10:30-11 a.m.	BREAK
11 a.m.-Noon	Assessment and Treatment of Panic Disorder, Agoraphobia, and Generalized Anxiety Disorder
Noon-1 p.m.	LUNCH
1-2:30 p.m.	Assessment and Treatment of Obsessive-Compulsive Disorder
2-3:30 p.m.	BREAK
3-4:30 p.m.	Assessment and Treatment of Obsessive-Compulsive Disorder

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REGISTRATION FORM

Note: Please indicate below which conference you are attending. Room reservations must be made with the respective hotels.

Crisis in Mental Retardation ___ May 19-20, 1986 (For room reservations, The Hilton, Albany, Albany (518) 462-6811 by May 15)

Treatment of Anxiety Disorders ___ (For room reservations, Ramada Inn, Syracuse,

CRISIS IN MENTAL RETARDATION

I am interested in
( ) AACME Continuing Medical Education Credit
( ) APA Continuing Continuing Credit
( ) NASW Continuing Education Credit
( ) 1 Academic Credit Hour

APPENDIX D
INDIVIDUALS INTERVIEWED BY THE PANEL

INDIVIDUALS INTERVIEWED BY PANEL MEMBERS*

Name	Date	Place of Interview
Stephen E. Breuning, Ph.D. Polk Center Polk, Pennsylvania	11/22/85	Rockville, Maryland
Vicky J. Davis Polk Center Polk, Pennsylvania	10/16/85	"
University of Pittsburgh		
Patrick Ackles, Ph.D. Former Post-Doctoral Fellow	6/26/85	Pittsburgh, Pennsylvania
Norman P. Curthoys, Ph.D. Chairperson, University Hearing Board	6/25/85	"
Nancy Day, Ph.D. Department of Psychiatry Member, Ad Hoc Committee	6/25/85	"
Thomas Detre, M.D. Senior Vice President for Health Sciences School of Medicine	6/25/85	"
Wilda DiPietro Former secretary to Dr. Breuning	3/19/86	"
Leonard Epstein, Ph.D. Department of Psychiatry Chairperson Preliminary Investigating Committee	6/25/85 3/19/86	" "
Janice L. Forster, M.D. Physician, John Merck Program for Multiply Disabled Children	6/25/85	"
Sue Ann Fultz Research Assistant, John Merck Program for Multiply Disabled Children	6/25/85	"
Carol Kaufman Research Administrator Western Psychiatric Institute and Clinic	3/19/86	"

*One or more Panel members participated in these interviews.

Name	Date	Place of Interview
David Kupfer, M.D. Professor and Chairman Department of Psychiatry	6/25/85 3/19/86	Pittsburgh, Pennsylvania "
Karen Matthews, Ph.D. Department of Psychiatry Member, Ad Hoc Committee	6/25/85	"
Robert Miller, Ph.D. (deceased) Department of Psychiatry Chairperson, Ad Hoc Committee	6/25/85	"
Edward J. Nuffield, M.D. Former Acting Medical Director John Merck Program for Multiply Disabled Children	6/25/85	"
Lori Sisson Former Senior Research Assistant	6/25/85	"
University of Illinois		
Robert L. Sprague, Ph.D. Director, Institute for Child Behavior and Development University of Illinois at Urbana-Champaign	4/19/85	New York, New York
Coldwater Regional Center for Developmental Disabilities		
Joyce Burns, Ph.D. Staff Psychologist	5/22/85	Coldwater, Michigan
Salvatore Cullari, Ph.D. Former Staff Psychologist	6/13/85	Boston, Massachusetts
Neal Davidson, Ph.D. Director of Psychology	4/19/85	New York, New York
Donald G. Ferguson, Ph.D. Former Staff Psychologist	5/21/85	Duluth, Minnesota
Ronald Hindbaugh, Ph.D. Director of Programs	5/22/85	Coldwater, Michigan
Bonita Hoffner, Ph.D. Former Staff Psychologist	5/22/85	"

Name	Date	Place of Interview
Jan Laurimore Former Secretary to Dr. Breuning	5/22/85	Coldwater, Michigan
Wesley Lyle Licensed Practical Nurse, Building 42	5/22/85	"
Robert Niblette, Ph.D. Staff Psychologist	5/22/85	"
Robert Rogan Facility Administrator	5/22/85	"
John Scott Program Director	5/22/85	"
Philip M. Smathers Supervisor of Special Education Branch Intermediate School District	5/22/85	"
Timothy Smoker** Pre-vocational & Vocational Coordinator Evergreen School	6/4/85	
Oakdale Regional Center for Developmental Disabilities		
John Regan, Ph.D.** Staff Psychologist	5/13/86	
University of North Carolina		
C. Thomas Gualtieri, M.D. Department of Psychiatry	6/26/85	Pittsburgh, Pennsylvania
Others		
Paul Koutnik, Ph.D.** Former Associate Professor of Education Department of Psychology Illinois Institute of Technology Chicago, Illinois	5/5/86	

Name	Date	Place of Interview
Johnny L. Matson, Ph.D. Former Director of Research Learning Development and Special Education Department Northern Illinois University De Kalb, Illinois	6/13/85	Boston, Massachusetts
Alan Poling, Ph.D. Department of Psychology Western Michigan University Kalamazoo, Michigan	6/13/85	"
Alan Wolach, Ph.D.** Chairman Psychology Department Illinois Institute of Technology Chicago, Illinois	5/13/86	

**Telephone Interviews

APPENDIX E
SITES VISITED BY THE PANEL

Sites visited by the full Panel or representative Panel members:

Coldwater Regional Center for Developmental Disabilities
Coldwater, Michigan
May 22, 1985.

Western Psychiatric Institute and Clinic, University of Pittsburgh
Pittsburgh, Pennsylvania
June 25-26 and March 19, 1985.

APPENDIX F
INDIVIDUALS INTERVIEWED BY NIMH STAFF/CONSULTANT INVESTIGATOR

INDIVIDUALS INTERVIEWED BY NIMH STAFF OR CONSULTANT INVESTIGATOR*

University of Pittsburgh

Name	Date
Richard M. Cohen, M.D. Former Chairperson Institutional Review Board	1/29/85
Michel Hersen, Ph.D. Member, Department of Psychiatry Investigating Committee	2/1/85
George Huber Legal Counsel	1/31/86
Robert E. Lee, M.D. Director of Presbyterian University Hospital Laboratories Chairperson, Investigating Committee School of Medicine	1/30/85
Donald F. Leon, M.D.** Former Dean, School of Medicine	3/15/85
Jessica H. Lewis, M.D. Former Chairperson, Institutional Review Board	1/30/85
John Thompson Director of Sponsored Project Administration Office of Research	10/18/84

Coldwater Regional Center for Developmental Disabilities

Henry Motes, Ph.D. Staff Psychologist	1/17/85
Monica Ross Chief, Medical Records	1/16/85
Ina Whitney Personnel Officer	1/16-17/85
Tim Wysocki, Ph.D.** Former Assistant in Psychological Services	5/20/85

*The names of individuals also interviewed by Panel members are not repeated here.

**Telephone interviews.

Oakdale Regional Center for Developmental Disabilities

Name	Date
Isak O. Berker, M.D. Medical Director and Chairman, Research Committee	5/14/85
James J. Coleman, Ed.D. Former Director of Normalization & Treatment	5/17/85
Cora Crow Resident Records Coordinator	5/14/85
Karen Demko Director of Program Services	5/16/85
Kay Kovac Secretary to Dr. David Ethridge, Facility Director	5/14/85
Jody R. Lewis** Michigan Department of Mental Health Former Health Assistant at Oakdale	8/13/86
M. Lombard, Ph.D. Staff Psychologist	5/14/85
David A. Nolley, Ph.D.** Former Coordinator of Psychological Services	5/14/85
Doris Rolland Principal Woodside Elementary School	5/15/85
Christine Schroeder, Ph.D. Staff Psychologist	5/17/85
John VanBuren Personnel Director	5/14/85
Alice Winton Audiologist	5/17/85

University of Illinois at Urbana-Champaign

Name	Date
Nina Almy, Ph.D. Staff Assistant to the Institutional Review Board	10/16/84
Douglas A. Bernstein, Ph.D. Chairperson, Investigating Committee	10/16/84

Theodore L. Brown, Ph.D. Vice Chancellor for Research and Dean of the Graduate College	10/16/84
Elaine Copeland Associate Dean of the Graduate College	10/15/84
Jack Kamerer Director of Grants & Contracts and Assistant for Business Affairs	10/15/84
Robert Linn, Ph.D. Member, Investigating Committee	10/16/84
Martin Maehr, Ph.D. Member, Investigating Committee	10/15/84
Karl M. Newell, Ph.D. Chairperson, Institutional Review Board	10/16/84

University of North Carolina

Name	Date
Stephen R. Schroeder, Ph.D. Research Scientist Department of Psychiatry	1/3/85

Other

Name	Date
Kenneth Gadow, Ph.D.** Assistant Professor Office of Special Education State University of New York, Stoney Brook	8/5/86
David Lyon, Ph.D.** Chairperson, Department of Psychology Western Michigan University	10/10/86
Fred Morris, R.N.** Former Director Calhoun County Community Mental Health Program Battlecreek, Michigan	5/21/86
William Sullivan U. S. Department of Education Washington, D. C.	10/12/84

APPENDIX G
SITES VISITED BY THE CONSULTANT INVESTIGATOR

Sites visited by the Consultant Investigator:

University of Illinois at Urbana-Champaign
Champaign, Illinois
October 15-6, November 26-27, November 30, December 4, 1984.

Coldwater Regional Center for Developmental Disabilities
Coldwater, Michigan
October 17, 1984, January 15-18, 1985.

University of Pittsburgh
Pittsburgh, Pennsylvania
October 18-19, 1984, January 29 - February 1, 1985.

University of North Carolina
Chapel Hill, North Carolina
January 2-3, 1985.

Oakdale Regional Center for Developmental Disabilities
Lapeer, Michigan
May 14-17, 1985.

APPENDIX H
PUBLICATIONS REVIEWED BY THE PANEL

PUBLICATIONS REVIEWED BY THE PANEL

DYSKINESIA STUDIES

Breuning, S.E., Ferguson, D.G., and Cullari, S. Analysis of Single-Double Blind Procedures, Maintenance of Placebo Effects, and Drug-Induced Dyskinesias With Mentally Retarded Persons. Applied Research in Mental Retardation, 1980, 1, 175-192.

Breuning, S.E., Ferguson, D.G., and Cullari, S. Analysis of Single, Double-Blind Procedures, Maintenance of Placebo Effects, and Drug-Induced Dyskinesia with Mentally Retarded Persons - A Brief Report. Psychopharmacology Bulletin, 1981, 17, No. 1, 122-123.

Gualtieri, C.T., Breuning, S.E., Schroeder, S.R., and Quade, D. Tardive Dyskinesia in Mentally Retarded Children, Adolescents, and Young Adults: North Carolina and Michigan Studies. Psychopharmacology Bulletin, 1982, 18:1, 62-5.

Breuning, S.E. Time Course of Tardive Dyskinesia in the Mentally Retarded: A Longitudinal Analysis. Abstract submitted (and later withdrawn) for presentation at the annual meeting, American College of Neuropsychopharmacology, 1983.

Gualtieri, C.T. and Breuning, S.E. A Behavioral Analogue of Withdrawal Dyskinesia, Submitted to Psychopharmacology, 1983 (withdrawn in December 1983 by the first author).

DYSKINESIA ASSESSMENT INSTRUMENT

Sprague, R.L., Kalachnik, J.E., Breuning, S.E., Davis, V.J., Ullman, R.K., Cullari, S., Davidson, N.A., Ferguson, D.G., and Hoffner, B.A. The Dyskinesia Identification System-Coldwater (DIS-Co): A Tardive Dyskinesia Rating Scale for the Developmentally Disabled. Psychopharmacology Bulletin, 1984, 20, No. 2, 328-338.

ADMINISTRATIVE REVIEW OF DRUG TREATMENT

Ferguson, D.G., Cullari, S., Davidson, N.A., and Breuning, S.E. Effects of Data-based Interdisciplinary Medication Reviews on Prevalence and Pattern of Neuroleptic Drug Use with Institutionalized Mentally Retarded Persons. Education and Training of the Mentally Retarded, April 1982, 103-108.

Ferguson, D.G., Cullari, S., and Breuning, S.E. Reduction of Psychotropic Medication Usage Through an Interdisciplinary Team Review Process. Proceedings of the Minnesota Conference on the Use of Medications in Controlling the Behavior of the Mentally Retarded, September 1980.

PHARMACOLOGIC TREATMENT STUDIES

Breuning, S.E., O'Neill, M.J., Ferguson, D.G. Comparison of Psychotropic Drug, Response Cost, and Psychotropic Drug plus Response Cost Procedures for Controlling Institutionalized Mentally Retarded Persons. Applied Research in Mental Retardation, 1980, Vol. 1, 253-268.

Breuning, S.E. and Davidson, N.A. Effects of Psychotropic Drugs on Intelligence Test Performance of Institutionalized Mentally Retarded Adults. American Journal of Mental Deficiency, 1981, 85:6, 575-579.

Breuning, S.E., Ferguson, D.G., Davidson, N.A., and Poling, A.D. Intellectual Performance of Mentally Retarded Drug Responders and Nonresponders. Archives of General Psychiatry, March 1983, 40, 309-13.

EFFECTS OF THERAPEUTIC MANIPULATION ON TASK PERFORMANCE

Wysocki, T., Fuqua, W., Davis, V.J., and Breuning, S.E. Effects of Thioridazine (Mellaril) on Titrating Delayed Matching-to-Sample Performance of Mentally Retarded Adults. American Journal of Mental Deficiency, 1981, 85:5, 539-547.

Davis, V.J., Poling, A.D., Wysocki, T., and Breuning, S.E. Effects of Phenytoin Withdrawal on Matching to Sample and Workshop Performance of Mentally Retarded Persons. The Journal of Nervous and Mental Disease, 1981, Vol. 150, No. 11, 718-725; and Psychopharmacology Bulletin, 1982, Vol. 18:1, 51-54.

Breuning, S.E. An Applied Dose-Response Curve of Thioridazine with the Mentally Retarded: Aggressive, Self-Stimulatory, Intellectual, and Workshop Behaviors - A Preliminary Report. Psychopharmacology Bulletin, 1982, 18:1, 57-59.

Breuning, S.E., Davis, V.J., Matson, J.L., and Ferguson, D.G. Effects of Thioridazine and Withdrawal Dyskinesias on Workshop Performance of Mentally Retarded Young Adults. American Journal of Psychiatry, 1982, 139:11, 1447-1454.

Breuning, S.E., Sisson, L.A., Fultz, S.A., Marshall, T., and Bregman, J.D. Effects of Neuroleptic Drugs on Titrating Delayed Matching-to-Sample Performance of Mentally Retarded Children. Submitted to Psychopharmacology, unpublished.

Breuning, S.E. and Poling, A.D. Pharmacotherapy. In J.L. Matson and R.P. Barrett (Eds.), Psychopathology in the Mentally Retarded, New York, Grune and Stratton, 1982, 195-251.

MULTISTATE SURVEY OF THE INSTITUTIONALIZED RETARDED

Davis, V.J., Cullari, S., and Breuning, S.E. Drug Use in Community Foster-Group Homes; in S.E. Breuning & A.D. Poling (Eds.), Drugs and Mental Retardation, Springfield, Ill., Charles C Thomas, 1982, 359-376.

REVIEWS

Breuning, S.E. and Poling, A.D. Pharmacotherapy. In J.L. Matson and R.P. Barrett (Eds.), Psychopathology in the Mentally Retarded, New York, Grune and Stratton, 1982, 195-251. (Also listed under Effects of Therapeutic Manipulation on Task Performance, above.)

Ferguson, D.G. and Breuning, S.E. Antipsychotic and Antianxiety Drugs. In S.E. Breuning and A.D. Poling (Eds.), Drugs and Mental Retardation. Springfield, Ill., Charles C Thomas, 1982, 168-214.

Breuning, S.E., Davis, V.J., and Poling, A.D. Pharmacotherapy with the Mentally Retarded: Implications for Clinical Psychologists. Clinical Psychology Review, 1982, 2, 79-114.

Barrett, R.P. and Breuning, S.E. Assessment of Intelligence, in J.L. Matson and S.E. Breuning (Eds.), Assessing the Mentally Retarded, New York, Grune & Stratton, 1984.

Sisson, L.A. and Breuning, S.E. Assessing Medication Effects, in J.L. Matson and S.E. Breuning (Eds.), Assessing the Mentally Retarded, N.Y., Grune and Stratton, 1984.

STIMULANT DRUG USE WITH MENTALLY RETARDED CHILDREN

Poling, A. and Breuning, S.E. Effects of methylphenidate on the fixed ratio performance of mentally retarded children. Pharmacology, Biochemistry and Behavior, 1983, 18:541-4.

Breuning, S.E., Ackles, P.K., and Poling, A. Dose-dependent effects of methylphenidate on the fixed-ratio performance of hyperactive severely mentally retarded adolescents. Manuscript submitted to Applied Research in Mental Retardation.

APPENDIX I
ANALYSES OF PUBLICATIONS

DYSKINESIA STUDIES

Breuning, S.E., Ferguson, D.G., and Cullari, S. Analysis of Single-Double Blind Procedures, Maintenance of Placebo Effects, and Drug-Induced Dyskinesias With Mentally Retarded Persons. Applied Research in Mental Retardation, 1980, 1, 175-192.

PHS grant cited: MH-32206

Authors' description and findings: Subjects were 10 (5 male, 5 female) institutionalized mentally retarded persons receiving thioridazine, chloropromazine, or haloperidol. Each subject was from a different living unit. The age range was from 17-71 years and the IQ range was 14-74. Informed consent was obtained for all participants. Drug withdrawal was planned for each subject by an interdisciplinary team.

The residents were randomly assigned to 1 of 5 sequences of treatment presentations with the restriction that each sequence have two residents. The first 4 sequences were designed to examine placebo effects and the 5th sequence was designed to examine the effectiveness of a procedure for discontinuing placebo and double-blind conditions. Each of the 5 sequences consisted of a combination of the following conditions: (1) drug; residents were receiving the medication (D); staff told medication is placebo (PD); (3) residents blind (RB); (4) staff blind (SB); (5) neither residents nor staff blind (NB); (6) both residents and staff blind (RSB).

Subjects 1-8 received medication for the first 8 weeks of the study. Subjects 9-10 received medication for the first 4 weeks of the study. Each subject was abruptly withdrawn from medication on the last day of week 8 for subjects 1-8 and the last day of week 4 for subjects 9-10. Throughout the remainder of the study the 10 subjects were off all medication. Drug conditions in which placebos were administered followed procedures identical to those used during medication conditions including abrupt withdrawal. The clinic nurse (LPN) or shift supervisor administered the medication. The nurse and supervisor were unaware of the study and received the same condition information presented to the living unit staff. All medications and placebos were similar in taste and appearance and were supplied in identical packages by the pharmacist and physician.

Target behaviors of participants were physical aggression, property destruction, disruption, and yelling-screaming. Frequencies of inappropriate behaviors were recorded by the living unit staff in 30-minute intervals, 24 hours per day. Reliability checks were made on a random selection of 4 30-minute intervals per day.

All subjects were assessed for dyskinesia 3 days prior to the discontinuation of medication (baseline) and at weekly intervals throughout the remainder of the study. Assessments were completed independently by 2 registered nurses using the Withdrawal Emergent Symptom Checklist.

The results showed that during the D condition the frequencies of inappropriate behaviors were relatively stable with no upward or downward trends. During the first RSB condition frequencies were lower than those obtained during the D condition with stabilization occurring by the end of the condition. During the PD, RB, NB, and SB conditions the frequencies were higher than those obtained during the D and SRB conditions. The reliability between observers and living-unit staff was between 87.6 and 93.8 percent across all conditions except the PD and RB conditions. During these conditions the frequencies of inappropriate behaviors recorded by the living-unit staff were substantially higher than frequencies recorded by the observers.

The authors note that the results empirically demonstrate the importance of using reliability checks, placebo conditions, and double-blind conditions in assessing medication effects with mentally retarded persons. Without placebo and double-blind conditions there was an unreliable increase in the recorded frequencies of the participant's inappropriate behaviors during PD and RB conditions and a reliable increase in the frequencies recorded during the SB and NB conditions. These increases are due to variables other than the medication being discontinued. The increases in frequencies during the PD and RB conditions are explained in terms of expectancy effects by staff. The increases of frequencies during the SB and NB conditions were due to operant variables.

Withdrawal dyskinesias were present in 9 of the 10 subjects and persistent dyskinesias (1.5 year followup) were present in 6 of the 10 subjects.

Relation to other studies: This is the same study as the one listed immediately below.

Panel comments: No plausible site for the execution of this study has been identified. When questioned by the Panel as to where this specific study had been conducted, Dr. Breuning said that it had been conducted at the Coldwater and Oakdale Regional Centers. In response to a letter, dated February 12, 1986, from the Panel requesting information about the specific site for the conduct of the study, Dr. Breuning again stated that it had been conducted at the Oakdale and Coldwater Regional Centers.

In the Panel's interviews with the coauthors, however, Drs. Ferguson and Cullari stated that Dr. Breuning had told them that the data had been collected at the Oakdale Regional Center. While the coauthors had been shown graphs by Dr. Breuning, they had not seen any raw data. Dr. Ferguson said that he had discussed the data with Dr. Breuning and had written portions of the manuscript. In discussing this study with members of the Panel, Dr. Cullari said that Dr. Breuning had brought the data from Oakdale and that the followup data had been obtained by "contacts" at Oakdale. Dr. Cullari indicated that he had conducted the literature search on placebos.

Extensive interviews with Dr. Breuning's coworkers at Oakdale did not identify anyone who had direct knowledge of research involving human subjects that had been conducted at Oakdale by Dr. Breuning. Dr. John Regan, Staff Psychologist at Oakdale, indicated that Dr. Breuning had only conducted research with goldfish while he was employed there.

Dr. Breuning's coworkers at the Coldwater Regional Center were not aware of any studies conducted there in which placebo/double-blind procedures had been used. In Panel interviews conducted with administrative staff at Coldwater, Mr. Robert Rogan, Facility Administrator, stated that medication manipulation for research was not permitted at Coldwater. Dr. Breuning did tell the Panel, however, that placebos, generally similar in appearance to medications, were used at Coldwater. He said that early in his tenure there they had not been obtained through the pharmacy but had been made up on his unit. He said he had not known of any policy prohibiting this procedure.

Panel findings: The reader is led to believe that the study was conducted at Coldwater Regional Center where Dr. Breuning and the coauthors were employed. Although the published report describes a fairly elaborate experimental design, including placebo administration, extensive behavioral observations over a 28-week period, and the collaboration of several trained observers, the Panel could find no evidence that the study had been conducted at either the Coldwater or Oakdale Regional Centers. The Panel concluded that the study described was not carried out.

Breuning, S.E., Ferguson, D.G., and Cullari, S. Analysis of Single, Double-Blind Procedures, Maintenance of Placebo Effects, and Drug-Induced Dyskinesia with Mentally Retarded Persons - A Brief Report. Psychopharmacology Bulletin, 1981, 17, No. 1, 122-123.

PHS grant cited: MH-32206

This is a brief version of the research described and discussed immediately above. There are minor differences in the two reports. This article reports subject ages as 17-74, and lists the abbreviation of one of the conditions in a slightly different way.

Gualtieri, C.T., Breuning, S.E., Schroeder, S.R., and Quade, D. Tardive Dyskinesia in Mentally Retarded Children, Adolescents, and Young Adults: North Carolina and Michigan Studies. Psychopharmacology Bulletin, 1982, 18:1, 62-5.

PHS grant support cited: None. However, this study is listed in the progress report for 2 R01 MH-32206-06 (submitted in June 1983), was published in an NIMH-sponsored journal, and was the basic study about which questions were raised, leading to this investigation. Gualtieri and Breuning (1983) uses data from this study and does cite PHS grant support.

Authors' description and findings: (Two studies are reported - Michigan - Breuning, and North Carolina - Gualtieri; only the Michigan data have been questioned and are discussed here.)

Michigan study - Fifty-seven subjects were studied at the Coldwater Regional Center, 28 males and 29 females, age range 12-71 (mean 25.7), IQ range 14-74 (mean 40.4). Subjects received comprehensive neurologic and developmental assessments with special attention to neurologic or developmental problems which might be associated with dyskinetic movements, stereotypies, or psychotic mannerisms which may have antedated neuroleptic treatment. Subjects were then withdrawn from neuroleptics with serial examinations for dyskinesia, behavior change, or non-dyskinetic withdrawal symptoms. Dyskinetic movements were assessed weekly - at baseline, during withdrawal, and for 80 weeks thereafter, using the Withdrawal Emergent Symptom Checklist (WESC) rating scale and examination. Interrater reliability is reported as 0.79 (Cohen's Kappa), implying more than one rater and systematic assessments.

Dyskinetic movements were reported as maximal at 4 weeks after withdrawal; 36 of 57 (63 percent) of the subjects exhibited symptoms. Dyskinetic movements were noted in 30 (53 percent) at 16 weeks and in 18 (32 percent) at 52 and 80 weeks.

Relation to other studies: Breuning (abstract, 1983) reported a 2-year followup of 45 of these subjects; Gualtieri and Breuning (1983) reported on 8 of these subjects who exhibited a behavioral analog of dyskinesia. The Panel comments here necessarily include some discussion of the followup study.

Panel comments: Unlike most of the other studies reviewed by the Panel, this article specifically states that "Fifty-seven subjects were studied at the Coldwater Regional Center." Dr. Breuning went there in September 1978, and left in January 1981, a period of 2 years and 4 months, or 108 weeks. This study reports data collected across 96 weeks; the followup reports a 3.5 year effort.

While at Coldwater, Dr. Breuning was assigned as a staff psychologist to Building 42. The age range of patients in that building was 10-26; subjects in the study ranged from 12-71. Panel members confirmed, however, that Dr. Breuning had access to medical records of all patients, and they interviewed a staff member who had observed Dr. Breuning testing patients from other buildings and who thought that some attendants had collected materials for Dr. Breuning. The Panel was told that Dr. Breuning collaborated with others and stimulated research outside of Building 42. A random review of charts of Building 42 patients by Panel members indicated that behavioral observations were carefully and frequently recorded. Some records included psychological assessments by Dr. Breuning. A few of the records included tardive dyskinesia records. The Panel also confirmed that the center was following a drug reduction policy while Dr. Breuning was there.

Regarding the reported comprehensive neurological assessments, the Panel was told by Dr. Neal Davidson, the center's Director of Psychological Services, that residents on admission received a comprehensive physical examination that could have included neurological assessment. Those needing specific neurological examination were sent to Ann Arbor. Dr. Breuning did not have the authority to order such examinations. The physician assigned to Building 42 during Dr. Breuning's tenure, Dr. Carlos Budding, had returned to Argentina and could not be questioned on this point.

Evidence regarding use of placebos in these studies is conflicting. This study does not refer to placebos; the followup to it reports withdrawal from medication under placebo and double-blind conditions. Center officials insisted that placebo/double-blind procedures would not have been carried out at Coldwater. Dr. Breuning told the Panel that placebos had been made up in the Coldwater pharmacy later; earlier they had been made up on his unit with capsules he thought they had bought at a Chicago supply house. Such placebos were similar, rather than identical, and were made up without a physician's order.

When questioned about the reported interrater reliability, Dr. Breuning said that he had done most of the assessments but that "periodically I would pick someone else."

The validity of this study was first questioned in late 1983, after Dr. Breuning had left Coldwater, when Dr. Robert Sprague raised questions regarding the collection of data for the followup study. After telephone discussion with Dr. Breuning about the discrepancy, Dr. Sprague asked Dr. Breuning, by letter, names or ID numbers of subjects, sex, age at beginning of study, dates of evaluation, and the names or initials of evaluators at 2-year followup or a 4-month followup reported by Dr. Breuning.

Dr. Breuning replied in a letter of December 7, 1983, that he was providing

> ... a copy of the information I have located. This includes (a) age, sex, IQ, medication, medication dosage, and years on medication dosage for the 24 clients, and (b) baseline, weeks 1, 4, 8, 16, 52, 80 and 96 WESC data. All I could locate was the raw data for the last assessment (96) on these clients and WESC summary data for weeks 1, 4, 8, 16, and 52. (These data were made available to the Panel.) Two points warrant comment. First, I have yet to locate the raw data or the subject identification code sheet. This information is now 3 years old and has not been reviewed in some time....

When asked about this letter by the Panel, Dr. Breuning said, "Well, he sent me an odd letter asking for either all of this or something on any 24 people. So I sent them something on any 24." Dr. Breuning maintained that he had told Dr. Sprague that "what we couldn't locate was systematic followup data because there weren't any..."(He maintained followup data were collected casually; this is discussed under Breuning, 1983, below.) Dr. Breuning also told the Panel that he had discarded the raw data some 6-12 months before Dr. Sprague's request. Dr. Breuning could not explain why he had written Dr. Sprague a letter implying that he couldn't locate the data if he had discarded them.

Dr. Gualtieri said he offered to go to Coldwater, review records, and attempt to substantiate at least parts of the research. Dr. Breuning indicated such a review would be impossible. When, sometime after receiving the summary data, Dr. Gualtieri asked for raw data, he was told by Dr. Breuning that they were lost.

According to Dr. Gualtieri, he met Dr. Breuning in 1980 when he visited Dr. Sprague's research program at Urbana-Champaign. Each was interested in the work of the other, but the opportunity for collaboration for publication came on the occasion of a panel organized by Dr. Breuning for the 1981 meeting of the New Clinical Drug Evaluation Unit (NCDU). In preparation for this panel, Dr. Gualtieri said he shared with Dr. Breuning results of his neuroleptic withdrawal study and subsequently learned from Dr. Breuning that his study of 57 subjects "at Coldwater" replicated Dr. Gualtieri's findings. Dr. Gualtieri said he then presented the North Carolina and parallel Michigan results and that the report was subsequently published in the Psychopharmacology Bulletin.

According to Dr. Breuning, he had shared summary WESC data with Dr. Gualtieri who did all of the analyses and wrote the NCDU presentation, attributing the work to Coldwater. Dr. Breuning said that he did correct the draft, but did not think the matter important. According to Dr. Breuning, he never told either Drs. Gualtieri or Sprague where the data came from. This contradicts information received from them. Dr. Gualtieri, in a written memo, said Dr. Breuning told him all 57 subjects were from Coldwater.

In reviewing correspondence between Drs. Breuning and Sprague regarding the latter's questions about the followup to this study, the Panel found no indication that Dr. Breuning ever suggested to Dr. Sprague that the basic study included data from a site other than Coldwater. When questioned by the Panel, Dr. Breuning said that at least some of the 57 subjects were at Oakdale.

The improbability of Dr. Breuning's having conducted any systematic research with human subjects while at Oakdale is discussed above in relation to that site and in the discussions of other studies.

Dr. Gualtieri wrote the Editor of the Psychopharmacology Bulletin, informing him that Dr. Breuning had advised him of certain irregularities in the Michigan data and asking the Editor to retract those parts of the paper referring to the Michigan data or making surmises or conclusions based on comparisons involving the Michigan data.

Panel findings: While the Panel found evidence that Dr. Breuning had done some assessments at Coldwater, the Panel concluded that there were serious irregularities in this study. The absence of significant portions of raw data and of identifiers for subjects for which there were data, the admitted lack of formality in the assessments, the contradictions, the final claim that subjects came from both Coldwater and Oakdale, and

and the improbability that identical protocols could have been carried out at both institutions led the Panel to conclude that any data that might have been collected were deliberately misrepresented and that the described study was not carried out.

Breuning, S.E. Time Course of Tardive Dyskinesia in the Mentally Retarded: A Longitudinal Analysis. Abstract submitted (and later withdrawn) for presentation at the annual meeting, American College of Neuropsychopharmacology, 1983.

PHS grant support cited: None. However, the study to which this is a follow-up was cited in the progress report on 2 R01 MH-32206-06, and questions regarding the authenticity of this abstract triggered this investigation. Gualtieri and Breuning (1983), does cite PHS grant support and uses data from the same study as does this one.

Authors' description and findings: Fifty-seven mentally retarded clients, 28 male and 29 female, receiving long-term treatment with a single neuroleptic and having no history with other medications (e.g., anticolinergic, antiepileptic), were withdrawn from their medication under placebo and double-blind conditions, maintained drug free, and rated for abnormal movements. Each client was mentally retarded (mean IQ 40) due to unknown etiology and had no identifiable neurological disorder. The presence of dyskinesias and nondyskinetic withdrawal symptoms was assessed weekly, by means of the Withdrawal Emergent Symptom Checklist (WESC). Assessments began 4 weeks prior to drug discontinuation and continued for 80 consecutive weeks following drug discontinuation. Assessments were conducted on 45 of the clients at 6-month intervals for an additional 2 years; i.e., 45 clients were followed for 3.5 years. Thirty-three percent showed no withdrawal problems; 35 percent showed nondyskinetic withdrawal symptoms, e.g., weight loss; 60 percent showed dyskinesias by the fourth week post-discontinuation; and 32 percent persisted in showing dyskinesias after the 16th week post-discontinuation. Only 7 percent showed dyskinesias prior to drug discontinuation, i.e., maintenance onset. Persistent dyskinesias were primarily (83 percent) characterized by moderate to severe movements, while withdrawal dyskinesias were 65 percent mild and 35 percent moderate to severe. The greatest proportion of clients having withdrawal dyskinesias had their dyskinesias cease to occur between the 12th and 16th week after drug discontinuation. Clients having dyskinesias cease to occur after week 16 were primarily those having mild dyskinesias which disappeared irregularly between weeks 16 and 52. No further change occurred after the 52nd week. Ninety-four percent of the clients with moderate to severe persistent dyskinesias showed no changes after week 16.

Relation to other Studies: See Panel comments, below.

Panel comments: This abstract of a proposed presentation for a symposium organized by Dr. Robert Sprague for the annual meeting of the American College of Neuropsychopharmacology (ACNP), December 1983, presents data from Gualtieri, Breuning, et al. (1982) and from a purported 2-year followup study on 45 of the same subjects. When Dr. Sprague learned that Dr. Breuning planned to present the followup data, he questioned Dr. Breuning's ability to collect such data after he had left Coldwater Regional Center which was identified in Gualtieri, Breuning, et al. as the site of the research. Dr. Breuning was at Coldwater from September 1978 to January 1981, a period of 2 years and 4 months; the basic study and followup required 3.5 years.

In response to Dr. Sprague's request for specific information and data (see Panel comments on Gualtieri, Breuning, et al. above), Dr. Breuning was able to provide "raw" followup WESC data on only 24 subjects, assessed once at week 96, with no subject identifiers. Copies of these data were made available to the Panel but proved of no use as they lack identifiers and are not of such a quality as to be considered research data.

In a letter to Dr. Sprague dated December 7, 1983, Dr. Breuning acknowledged "major problems" regarding data on the 45 subjects in the followup whom he identified as "individuals supposedly followed after I left Coldwater." He wrote, "The 24 clients were the ones I had personally assessed and thought might still be presentable at ACNP." Dr. Breuning gave the Panel a copy of the substantially amended abstract he had suggested as still presentable. It indicates only 24 clients were followed up at one additional 4-month interval. At Dr. Sprague's insistence, no data on this study were presented.

When Dr. Breuning was interviewed by the Panel, he characterized the statement in the abstract that, "Assessments were conducted on 45 of the clients at 6-month intervals for an additional 2 years," as "a very minor semantic error in the abstract..." and said "All I meant to say was, not implying methodological rigor... just saying that somebody periodically looked at these people at 6-month intervals and didn't see any evidence of change...," an approach quite discrepant from the "assessments" described in the abstract and the conclusions there about how many subjects had what type of change during the study. When asked what had happened to the reported 45 subjects, Dr. Breuning said, "I said (to Dr. Sprague) I would drop out all of the stuff that was a casual, you know, eyeball kind of thing and put in a shorter, systematic one-time rigorous followup." Dr. Breuning refused to identify the person who gave him the followup information, except to characterize him/her as a friend and a member of the Coldwater nursing staff, indicating that he himself took responsibility and that he did not want to get that person in trouble.

As discussed under Gualtieri, Breuning, et al. above, although the article describing the basic study stated it was carried out at Coldwater, Dr. Breuning told the Panel that some of the subjects were from Oakdale. The article on the basic study did not mention placebo/double-blind procedures; the abstract states they were used. The possibility of any such research having been carried out at Oakdale is discussed elsewhere. The conflicting evidence regarding use of placebos at Coldwater is discussed above.

Panel findings: The Panel found serious irregularities in the basic study of which this is the purported followup. The Panel regards the original abstract as a deliberate misrepresentation and attempt to mislead the ACNP program committee and annual meeting. The Panel doubts the existence of even casual followup data and does not find Dr. Breuning's explanation for not identifying his respondent credible. The Panel concluded that, as for the basic study, the described followup study was not conducted.

Gualtieri, C.T. and Breuning. S.E. A Behavioral Analogue of Withdrawal Dyskinesia, Submitted to Psychopharmacology , 1983, (withdrawn in December 1983 by the first author).

An abstract of this study, Gualtieri, C.T. and Breuning, S.E., Evidence for a Behavioral Analog of Tardive Dyskinesia, appeared in the December 1983 abstracts of papers presented at the annual meeting of the American College of Neuropsychopharmacology. The abstracts for the 1986 annual meeting contained the following note: "Dr. Thomas Gualtieri wishes to remove his name from the abstract entitled 'Evidence for a Behavioral Analog of Tardive Dyskinesia' published in the 1983 ACNP Annual Meeting Abstract Book."

PHS grant support cited: MH-32206, MH-30915 (and MH-33127 and HD-10570 to C.T. Gualtieri).

Authors' description and findings: Subjects were 51 young, institutionalized, mentally retarded individuals (26 male, 25 female), free from neurological disorders associated with dyskinesia, who had been treated with neuroleptics (Mellaril, Thorazine, and Haldol). They were rated on the Withdrawal Emergent Symptom Checklist 4 weeks prior to withdrawal from neuroleptic treatment and weekly for 80 weeks after withdrawal. Target behaviors (withdrawal dysbehavior, or WDB) were significant behavior problems arising during the postneuroleptic withdrawal period, different in kind and degree from those which initially warranted neuroleptic treatment, not associated with systemic symptoms of neuroleptic withdrawal, and the occurrence and subsidence of which was positively correlated with the temporal cause of dyskinesias. Interrater reliability was 0.86 (Cohen's Kappa). Interrater agreement on behavioral observations was above 98 percent.

Eight subjects exhibited patterns of behavior following neuroleptic withdrawal consistent with WDB. The authors hypothesize that withdrawal from long-term neuroleptic treatment was the occasion of behavioral instability and, in turn, may be the consequence of dopamine hypersensitivity in mesocortical and mesolimbic systems. The authors note that the phenomenon was observed in only a small number of subjects, that replication is required, and that the importance of their finding is strengthened by the rigorous design of the study and the high reliability of the instruments used.

Relation to other studies: Data reported here are from the study reported in Gualtieri, Breuning, Schroeder, and Quade (1982), above.

Panel comments: The first author, Dr. Gualtieri, in a written statement and in an interview with the Panel, indicated that he had clinical descriptions and had written a theoretical article on a behavioral analog of tardive dyskinesia. He had asked Dr. Breuning if, out of the 57 subjects studied at Coldwater and reported in Gualtieri, Breuning, et al., any had followed the pattern he had observed clinically of transient behavioral deterioration after neuroleptic withdrawal. He said that several months later he received from Dr. Breuning "magnificent" data on eight Coldwater subjects who showed unequivocally the pattern of postneuroleptic withdrawal behavioral instability. Dr. Gualtieri, who said that he saw only summary data, wrote the article. It was submitted to Psychopharmacology and was accepted for publication in October 1983. In December, when Dr. Sprague raised questions about Dr. Breuning's work, Dr. Gualtieri asked to review the patient records and raw data, and he asked the editor of Psychopharmacology to hold back publication of the article. Shortly thereafter, Dr. Breuning told Dr. Gualtieri that he was unable to locate any raw data or subject identifiers and that it would not be possible for Dr. Gualtieri to review patient records and data at Coldwater independently. Dr. Breuning agreed that the article should be withdrawn.

Panel findings: As for the parent study, Gualtieri, Breuning, et al,, and for the reasons stated in the findings for that study, the Panel concludes that any data that might have been collected were deliberately misrepresented and that the described study was not carried out.

DYSKINESIA ASSESSMENT INSTRUMENT

Sprague, R.L., Kalachnik, J.E., Breuning, S.E., Davis, V.J., Ullman, R.K., Cullari, S., Davidson, N.A., Ferguson, D.G., and Hoffner, B.A. The Dyskinesia Identification System-Coldwater (DIS-Co): A Tardive Dyskinesia Rating Scale for the Developmentally Disabled. Psychopharmacology Bulletin, 1984, 20, No. 2, 328-338.

PHS grant cited: MH-32206

Authors' description and findings: This article reviews scales previously developed for the diagnosis and assessment of tardive dyskinesia, criticizing them for their failure to include the developmentally disabled in subject populations used to establish norms. The development of the DIS-Co is described; normative data on 519 subjects at the Cambridge State Hospital, Cambridge, Minnesota, are presented; and percent of items that can be assessed in an institutional population, interrater reliability, stability over time, distribution of ratings by item in a large sample, and influence of patient cooperation are discussed. The scale was constructed in a format easy to follow, with nontechnical language, so it could be used by a wide range of raters and professionals. It achieved a high interrater reliability with nurse-raters who had been given a 12-hour training course in the use of the instrument.

Relation to other studies: None.

Panel comments: The development of a dyskinesia rating scale for developmentally disabled was one of the major activities carried out under grant MH-32206, awarded to the University of Illinois at Urbana-Champaign, with Dr. Robert L. Sprague as principal investigator. Formal pilot studies were carried out at Coldwater Regional Center where Dr. Breuning's role was described at that time by Dr. Sprague as "supervising all research done in conjunction with our project." Interviews at Coldwater, and separately with Drs. Sprague, Ferguson, Davidson, and Cullari, and with Ms. Vicky Davis confirmed the work at Coldwater. Ms. Davis made available summary minutes of Coldwater workgroup meetings and working papers used in developing the scale, and she confirmed that copies of DIS-Co ratings made available to the Panel by Dr. Sprague were her ratings from Coldwater.

Dr. Sprague told the Panel that the Cambridge State Hospital data were used in the validation study reported here because the sample was larger and better than that at Coldwater. Another explanation for exclusive use of the Cambridge data is the difference in interrater reliability; at Coldwater the total score on interrater agreement was 0.53, at Cambridge 0.78.

Panel findings: The Panel identified no issues regarding the reported study at Cambridge State Hospital. The inclusion of Dr. Breuning's name appears to be an acknowledgment of his role in the pilot studies at Coldwater.

ADMINISTRATIVE REVIEW OF DRUG TREATMENT

Ferguson, D.G., Cullari, S., Davidson, N.A., and Breuning, S.E. Effects of Data-based Interdisciplinary Medication Reviews on Prevalence and Pattern of Neuroleptic Drug Use with Institutionalized Mentally Retarded Persons. Education and Training of the Mentally Retarded, April 1982, 103-108.

PHS grant cited: MH-32206

Authors' description and findings: This article reports on a method developed at Coldwater Regional Center to reduce medication use by assessing medication responses in interdisciplinary team meetings held on a monthly basis. Frequency of inappropriate behaviors was the key measure, with trend lines established as a guide to adjustments in the prescription of medication.

Three of the five Coldwater treatment programs were studied. Program 1 had 70 male and female residents, ages 13-26, with approximately equal numbers of mildly, moderately, severely, and profoundly retarded individuals. It included some of the most severe behavior problems at the center. Programs 2 and 3 each had 80 male and female adults, mostly severely and profoundly retarded. All participants had been receiving a neuroleptic for at least 1 year.

Treatment teams for the programs, each of which included a physician, a psychologist, social workers, nurses, a program director, a pharmacist, and direct care staff and/or direct care supervisor, met monthly. Adaptive behaviors, dyskinesias, and withdrawal symptoms were discussed, but the frequency of inappropriate behaviors was the item upon which decisions regarding adjustments in medications were based. Charts displaying frequency of inappropriate behaviors were reviewed for each subject at team meetings. Mean daily frequency, mean deviation score, and a trendline were computed for each subject. Medications were reduced when the mean daily frequency of inappropriate behavior was stable within one standard deviation. Reductions were typically 25 percent to 50 percent per 30-day review period. No medication changes were ordered if the trend was decreasing. Dosage reductions began when the trend stabilized over a 30-day period, and reductions continued to the 0 mg. level or until there was an increase in inappropriate behaviors. If there was an increase in the trend of inappropriate behaviors, medications were increased by 25 percent to 50 percent increments until the trend stabilized or until a dosage equivalent to 800 mg. chlorpromazine daily was reached. Once frequencies were stabilized with dosage increases or decreases, that level of medication was maintained for 90 days before further changes were made. If the frequency of inappropriate behavior remained high at the maximum dosage level, medications were gradually reduced, the rationale being that high frequencies were better off drugs than on drugs. The evaluation of the behavior of individual subjects was based on 24-hour, 7-day weekly frequency counts conducted by direct care staff. All staff had received approximately 200 hours of general inservice training, of which 20 hours covered principles of behavior management.

Comparisons were made between two conditions over a period of 25 months: team meeting and no team meeting. Increases in medication dosage were observed when there was no meeting, and decreases were observed when there were meetings. The conclusion was that team meetings represented an efficient method of monitoring medication use based on objective measures and were economical of staff time. Further, it was reported that physicians relied on the team reports.

Relation to other studies: Breuning, O'Neill, and Ferguson (1980) is cited for a description of staff behavior rating procedure.

Panel comments: The three programs reported are those to which Drs. Breuning (Program 1), Cullari (Program 2), and Ferguson (Program 3) were assigned as staff psychologists. The data from the three programs are not pooled but reported separately. They cover 25, 12, and 18 months respectively.

Coauthor Ferguson told Panel members that this study had been generated by him in response to concern at the State level for objective review and reduction of medication. He had discussed this interest with another of the coauthors, Dr. Cullari, whose clinical responsibilities at Coldwater were similar to his own. Dr. Breuning had clinical responsibilities for a somewhat higher functioning population and, according to Dr. Ferguson, requested that data from his patients be included in the study. Dr. Ferguson said that he and Dr. Cullari had each done their own data analysis. The data were not pooled because of the differences in the populations. Dr. Ferguson said he had copies of the summary data sheets for his patients and for those of Dr. Cullari; Dr. Cullari confirmed this. Dr. Ferguson provided the Panel with minutes of meetings of his team. Drs. Ferguson and Cullari both said they had not seen Dr. Breuning's data sheets. Another Coldwater staff member expressed his belief that Dr. Breuning had made the observations.

The other coauthor, Dr. Davidson, Director of Psychological Services at Coldwater, also stated there was an interest at the State level in drug reduction and said that he had been aware of ongoing discussions among members of his department around this issue. He said that reports had been gathered on patient behavior on a 24-hour daily basis and that in-service training had been provided to staff. Panel members, who site visited Coldwater and examined a random sample of patient records, confirmed the existence of 24-hour behavioral observations.

Dr. Ferguson described this as an "informational study," and Dr. Davidson called it an "administrative study," indicating that it had not been regarded as subject to the same standards as a controlled study. The article contains some apparent inconsistencies. For example, the numbers of subjects vary from 250 in the article abstract to 230 total on the individual projects and to a maximum of 97 reported upon in the figures. This discrepancy was clarified by Dr. Ferguson's explanation that 250 represented the total pool of subjects at the beginning of the observation period, and 230 was the number on medication at that time. Some of the subjects were administratively transferred during the course of the observation period; it was decided to report only on those subjects for whom there was unbroken observation data, thus accounting for the numbers displayed in the figures.

While the article abstract states that the study "covered a consecutive 25-month period," only Program 1, that of Dr. Breuning, reports a period that long; the periods reported appear to extend somewhat beyond the respective coauthors' tenure at the center. Dr. Ferguson explained that baseline information, covering periods of from 2.5 to 4.5 months, was collected from patient records. A note at the end of the references following the article indicates that the study was terminated at different points because of center-wide resident reassignments.

Panel findings: Although it is possible that this study was carried out as reported, it was not possible to verify that data existed for that portion contributed by Dr. Breuning. Therefore, the Panel was not able to draw any conclusion regarding the validity of this study.

Ferguson, D.G., Cullari, S., and Breuning, S.E. Reduction of Psychotropic Medication Usage Through an Interdisciplinary Team Review Process. Proceedings of the Minnesota Conference on the Use of Medications in Controlling the Behavior of the Mentally Retarded, September 1980.

This is a conference presentation of the material presented in Ferguson, Cullari, Davidson, and Breuning, above.

PHARMACOLOGIC TREATMENT STUDIES

Breuning, S.E., O'Neill, M.J., Ferguson, D.G. Comparison of Psychotropic Drug, Response Cost, and Psychotropic Drug plus Response Cost Procedures for Controlling Institutionalized Mentally Retarded Persons. Applied Research in Mental Retardation, 1980, Vol. 1, 253-268.

PHS grant cited: MH-32206

Authors' description and findings: Subjects were 18 institutionalized mentally retarded persons from 4 living units, 11 female, 7 male, ages 17 to 71, with a mean IQ of 47, and a range of 19-64. Subjects had displayed inappropriate behaviors (physical aggression, property destruction, yelling (screaming), been designated for drug (thioridazine, chlorpromazine, mesoridazine, or lithium carbonate) discontinuation by an interdisciplinary team, and previously had been involved in a token reinforcement response cost program under which tokens were delivered on completion of a designated appropriate behavior and taken away upon designated inappropriate behavior. Data were collected in the living unit of each subject. Living units and their staffing are described in detail.

Subjects were randomly assigned to one of two treatment sequences: sequence 1 (11 subjects) was Drug (D-baseline), Drug + Response cost (D+RC); sequence 2 (7 subjects) was D (placebo CP), and RC. Drug withdrawal was over a 3-week period. Placebo/double-blind controls were in effect and were discontinued under a procedure described in Breuning, Ferguson, Cullari (1980) initiated at week 26 for sequence 1 and week 22 for sequence 2.

Frequencies of inappropriate behaviors were recorded at 30-minute intervals, 24 hours a day. Details of observational procedures and reliability checks are given. Subjects were assessed for dyskinesia and other withdrawal symptoms at baseline and 1-week intervals following drug discontinuation, using the Withdrawal Emergent Symptom Checklist.

The findings are reported with detailed tables and graphic displays of the data. In both sequences, target behaviors were significantly reduced in the response cost condition, with little change in any of the other conditions of drug, drug plus response cost, or placebo. Withdrawal dyskinesias and other withdrawal symptoms were observed in 13 of the 18 subjects, and dyskinesias persisted in 7 of the subjects at 1-year followup. It was argued that the findings proved that the medications most frequently prescribed to control behavior are not efficacious.

Relation to other studies: Breuning, Ferguson, and Cullari (1980) is cited for placebo/double-blind discontinuation procedures. Reference to interdisciplinary team-planned drug withdrawal is made in several studies, notably Ferguson, Cullari, Davidson, and Breuning, 1982, and Breuning, O'Neill, and Ferguson (1980) as are behavioral observations at 30-minute intervals 24 hours a day.

Panel comments: Dr. Ferguson, the first author, told Panel members that Dr. Breuning told him this study was conducted at Oakdale, and that Dr. Breuning had written up the methodology and prepared the graphs. He, Ferguson, had not seen primary data. He had helped with interpretation of the data and the writing of the manuscript. He said that he had written the introduction. He also said that he had questioned the methodology. It was his understanding that observations were made by clinical staff at Oakdale, with reliability checks by Dr. Breuning who would observe at the same time.

When asked about the several studies that he had coauthored with Drs. Ferguson and Cullari while they were all at Coldwater, Dr. Breuning told the Panel that, to the best of his knowledge, they were carried out at Oakdale and Coldwater. When asked why he had not indicated that data came from two sites, he indicated that he had simply carried over terse writing habits from his research with animals.

Interviews and record searches at Oakdale indicated that this study could not have been carried out there. While evidence on use of placebos at Coldwater is conflicting (see the site discussion above), it is inconceivable that a study of this complex design and duration could have been carried out there without the knowledge of supervisors or coworkers. While the Panel found evidence of a drug withdrawal program and behavioral observations, it found no evidence that a study as described here was carried out at Coldwater.

Panel finding: The Panel concluded for the above reasons that the study described was not carried out.

Breuning, S.E. and Davidson, N.A. Effects of Psychotropic Drugs on Intelligence Test Performance of Institutionalized Mentally Retarded Adults. American Journal of Mental Deficiency, 1981, 85:6, 575-579.

PHS grant cited: MH-32206

Authors' description and findings: Twenty-four institutionalized mentally retarded persons received intelligence tests under both standard and reinforcement conditions while on and off psychotropic medications. Medications included chlorpromazine, thioridazine, haloperidol, mesoridazine, and lithium carbonate. Informed consent from their parents or guardians was obtained for all participants. Participants were randomly assigned to one of four groups, with the restriction that there be six participants per group. Thirteen of the subjects were female, 11 male; ages ranged from 24-56.

All participants received three intelligence tests, with 60 days separating each test. For all three test administrations (various tests) for a given participant, the same test level and test form were used, and they were conducted by the same examiner.

The four groups were randomly assigned to one of four condition sequences. The first test was administered under standard testing conditions to the participants in each of the four groups. The second test was administered under standard testing conditions to Groups 1 and 3, and under reinforcement conditions to Groups 2 and 4. The first and second tests were administered while the participants in the four groups were receiving their medication. The third test was then administered under standard conditions to Groups 1 and 3 and under reinforcement conditions to Groups 2 and 4. At this time, the participants in Groups 1 and 2 were no longer receiving their medication, while the participants in Groups 3 and 4 remained on their medication.

The standard testing condition consisted of administration of the test as described in the test manuals. The reinforcement testing condition consisted of an individually selected consumable reinforcer being presented contingent upon correct responding to test items.

Medication was discontinued over a 3-week period (Groups 1 and 2), beginning on the day following the participants' second test. Each week the medication was reduced 33 percent, with complete discontinuation occurring the third week. All participants were placed on a placebo similar in taste and appearance to their medicine. At the time of the third test, all participants had been off the placebo for 2 weeks.

To help insure reliability, all examiners were unaware of the purpose of the study and whether a participant was receiving medication. Two test protocols per group, per test, were randomly selected and divided among three volunteer psychologists not involved in the study.

Results showed that when on medication there were no differences between IQs obtained under standard and reinforcement conditions. When participants were off medication, there were significant increases in scores obtained under both standard and reinforcement conditions. The increase in scores under reinforcement condition was 23 points greater than the increase obtained under the standard condition (increases of 30.2 and 6.9 points, respectively).

Relation to other studies: Breuning, Ferguson, and Cullari (1980) is cited as reference for placebo-discontinuation procedures. The placebo administration procedures are discussed in detail there.

Panel comments: The date of the paper, 1981, and the identification of the authors with the Coldwater Regional Center, imply that the study had been conducted at Coldwater. However, coauthor Davidson told the Panel that the study had not been carried out there and that the data had come from Oakdale. He and the Facility Administrator said that placebos was not used at Coldwater, although Dr. Breuning told the Panel that they had been used there. Dr. Davidson said that his role in the study was to review the literature and to work on drafts of the manuscript. He said that he had not seen raw data.

Interviews with officials and staff at Oakdale and searches of records indicated that this study could not have been carried out there (see site discussion, above). No consent forms for this study could be found at Oakdale or at Coldwater.

In a letter dated February 12, 1985, the Panel asked Dr. Breuning to identify specifically the site or sites where the data for this study had been collected. Dr. Breuning replied that the data were collected at many sites in Illinois and at Oakdale, but he could not recall or name the specific sites in Illinois.

Panel finding: The Panel was unable to identify a plausible site where this study might have been performed. For this reason and those discussed above, the Panel concludes that the described study was not carried out.

Breuning, S.E., Ferguson, D.G., Davidson, N.A., and Poling, A. Intellectual Performance of Mentally Retarded Drug Responders and Nonresponders. Archives of General Psychiatry, March 1983, 40, 309-13.

PHS grant cited: MH-32206

Authors' description and findings: In a prestudy trial, 142 individuals were studied under a drug-discontinuation regimen with 20 responders and 122 nonresponders identified by at least a 60 percent decrease or no change or increase in target symptoms (aggression, property destruction, screaming/yelling, etc.). Symptoms were recorded 24 hours per day in 30-minute intervals by living-unit staff. An ABA (no drug-drug-no drug) design was used.

In the study proper, 40 institutionalized mentally retarded adolescents (all receiving a DSM III diagnosis of undersocialized aggressive conduct disorder) were divided into thioridazine responders and nonresponders, with each group divided into four randomly assigned groups: standard testing versus reinforcement testing, under drug and nondrug conditions. Assessments were double-blind, placebo controlled.

IQ testing (Leiter international performance scale) was conducted three times on each subject, with 8 weeks between administrations 1 and 2 and 12 weeks between 2 and 3. The test administrations for each subject were by the same examiner. Five examiners were used, each randomly assigned eight subjects. Three test protocols per group, per test, were randomly selected and independently scored by three volunteer psychologists. In addition, six test administrations were randomly selected and viewed through a two-way mirrored window by one of the volunteer psychologists.

Individually selected consumable reinforcers were used. Primary target inappropriate behaviors were again physical aggression, property destruction disruption, and kicking screaming recorded at 30-minute intervals 24 hours per day in living units.

Reliability checks were made on a random selection of four 30-minute intervals per day during the morning shift and two during the afternoon. Informed consent was reported to be obtained from parents or guardians.

It was reported that subjects responded to the reinforcement condition with improved scores while off drugs but not while on drugs.

Relation to other studies: The basic paradigm is the same as in Breuning and Davidson (1981) which is cited. Ferguson has published a study in which the third experiment is based on this study (Ferguson, D.G., Effects of Neuroleptic Drugs on the Intellectual and Habilitative Behaviors of Mentally Retarded Persons. Psychopharmacology Bulletin, 18:1, 54-57).

Panel comments: Coauthor Ferguson told members of the Panel that he had not seen any raw data for this study, only graphs or figures prepared by Dr. Breuning, and that Dr. Breuning prepared his graphs at home. He said that he had thought a large portion of the study had been done at Oakdale and that it was continued at Coldwater, but he also said that he was unaware of any drug manipulation done at Coldwater.

Coauthor Davidson told members of the Panel that he had seen no data for this study, but that he had looked at the literature and worked on drafts. He said that he had been told by Dr. Breuning that the study had been carried out at Oakdale. He stated specifically that the work had not been done at Coldwater and denied the practice of giving placebos there. According to Dr. Breuning, placebos were used there informally. The Panel received minutes of meetings of a Coldwater treatment team which indicated use of a placebo. Dr. Davidson also indicated that the DSM-III was not used at Coldwater; according to the Facility Administrator, it was institutional policy to use the ICD-9.

In letters to the Panel and to the editor of Archives of General Psychiatry, coauthor Poling indicated that he had not seen raw data for the study, that he could not vouch for informed consents or how medications were arranged, and that he now had misgivings about the scientific merit of the study. In an interview with Panel members, he described his role in the study as discussing the design and working on data analysis and editing.

Extensive interviewing of staff at Oakdale indicated that this study could not have been done there. In their view, Dr. Breuning's schedule and lack of access to patient records in buildings other than the one in which he worked precluded such a study. While requests to the research committee for other proposed studies by Dr. Breuning were on file, there was no record of this study.

In a letter dated April 24, 1986, Dr. Breuning, responding to a specific question regarding the site of this study, wrote, "This data was collected at many sites in Illinois and at Oakdale. Due to the passage of time, the specific sites in Illinois cannot be recalled with exactitude...."

Panel findings: Given the size of the sample (142 in the prestudy drug trial), the complexity of the design, and the described behavioral recording at 30-minute intervals 24 hours per day, this study could not have been done in the Chicago area schools. All evidence from Oakdale and Coldwater indicates it could not have been carried out at either site. The Panel concludes that the described study was not carried out.

EFFECTS OF THERAPEUTIC MANIPULATION ON TASK PERFORMANCE

Wysocki, T., Fuqua, W., Davis, V.J., and Breuning, S.E. Effects of Thioridazine (Mellaril) on Titrating Delayed Matching-to-Sample Performance of Mentally Retarded Adults. American Journal of Mental Deficiency, 1981, 85:5, 539-547.

PHS grant cited: MH-32206

Authors' description and findings: The effects of thioridazine on the performance of a titrating delayed matching-to-sample discrimination by four mentally retarded adults were investigated. Each subject had received a particular daily dose of thioridazine for at least 150 days prior to the experiment. An interdisciplinary team of professionals, including a physician and a psychologist, had identified each of the subjects as a candidate for gradual withdrawal from the medication. Criteria for their selection were low frequency or low severity of inappropriate behavior and/or independent evidence that indicated specific environmental variables controlling the occurrence of existing inappropriate behavior. Subjects were receiving no other psychotropic or anticonvulsant medications. Informed consent was obtained from each subject's guardian, and the project was approved by the institution's research committee.

Testing sessions occurred in a room measuring 3.0 m. wide x 7.1 m. long. Trials began with the center of three response panels illuminated by one of three colors. The delay between depression of the center response panel and presentation of the two comparison stimuli on the side response panels varied according to the accuracy of the subject's performance.

The primary dependent variable was the limit of delay, defined as the longest delay at which the subject emitted four consecutive correct responses in a 30-minute session. The subject's chronic doses of thioridazine were reduced systematically in a multiple baseline across-subjects design. Biweekly assessments were made. For all of the subjects, the limit of delay increased after, and only after, reductions in daily thioridazine doses had been implemented.

Results indicated that the withdrawal of chronically administered thioridazine resulted in increased accuracy in a delayed matching-to-sample simple task, suggesting that the drug impairs performance of this discrimination.

Relation to other studies: While Breuning, O'Neill, and Ferguson (1980) is cited, this is a discrete study.

Panel comments: This multiauthored report is actually a publication of the material submitted by Dr. Wysocki, under Dr. Breuning's supervision, for his doctoral dissertation at Western Michigan University. In contrast to the style of most of the other papers reviewed by the Panel, it gives thanks to other staff for their help. The Panel verified that this study was conducted at the Coldwater Regional Center where a matching-to-sample-apparatus was in place in Building 42. Patients were tested with this equipment in connection with student dissertations and in the assessment of tardive dyskinesia and the development of the DIS-Co scale. Dr. Sprague provided the equipment for Dr. Breuning's use. The project was approved by the Coldwater Research Committee, and Coldwater staff interviewed by the Panel observed the testing of subjects. Ms. Davis told the Panel that her role had been to see that the matching-to-sample apparatus ran smoothly.

The thioridazine dosage was reduced according to a prearranged schedule. The rate of reduction is not stated but can be read from graphs of the data. Subjects S, T, and C follow dosage reduction schedules in which each subsequent dosage was less than the prior dosage. Subject J went from 400 mg. to 150 mg. to 300 mg. to 150 mg. to 0 mg. The time intervals were not standardized across subjects. One subject, C, showed a worsening of performance with the dosage decrement from 200 mg. to 100 mg.

The authors dismiss practice effects as a cause of their findings although the study was not designed to adequately assess this possibility. There is no control group, and at no time is a dosage decrement maintained long enough to see if improvement might have continued with maintenance of that new level. The patients may have been overmedicated, and a combination of dosage reduction and practice effect could be an alternative explanation along with any degree of "placebo" effect from knowing that dosages were being reduced. The observed performance changes occurred quickly after each dosage change, a somewhat unusual finding since tissue concentrations of thioridazine and its metabolite, mesoridazine, would not be expected to change as rapidly as these findings suggest.

Panel finding: The Panel confirmed that this study was carried out and found no information to suggest that it was conducted improperly.

Davis, V.J., Poling, A.D., Wysocki, T., and Breuning, S.E. Effects of Phenytoin Withdrawal on Matching to Sample and Workshop Performance of Mentally Retarded Persons. The Journal of Nervous and Mental Disease, 1981, 169:11, 718-25, and Davis, V.J., Psychopharmacology Bulletin, 1982, 18, 51-54.

PHS grant cited: MH-32206

Authors' description and findings: This article was based on research conducted by Ms. Davis at Coldwater Regional Center in partial satisfaction of the requirements for an M.A. degree from Western Michigan University. It describes the effects of the withdrawal of an antiepileptic medication on response performance on a matching-to-sample task of three mentally retarded persons and on workshop performance for two of them.

Subjects were three institutionalized mentally retarded persons who had been receiving phenytoin and no other antiepileptic or psychotropic medications for at least 3 years and who had been identified by an interdisciplinary team for gradual and systematic withdrawal from phenytoin on the basis of no observed seizure activity for 3 years or more. Two (D and L) were female, ages 27 and 23, and one (E) male, age 16. IQs were 30, 34, and 47 respectively. Informed consents were obtained.

Three initial matching-to-sample sessions were preexperimental. The test room and procedures are described in detail. The experiment began with the fourth session. Phenytoin doses were reduced for D from 100 mg. to 0. mg., and for L and E from 300 mg. to 150 mg. to 0 mg. An inactive placebo similar to phenytoin in taste and appearance was administered at the 0 mg. level. Matching-to-sample performance was assessed at all dose levels. Following matching-to-sample sessions, performance on a workshop assembly task (assembly of a 15-part Bendix RB-2 Coaster bicycle brake) was respectively analyzed for D and L. Three response measures were taken by the school (where the workshop was): percentage of time on task, number of assemblies completed, and number and type of prompts required. Four types of prompts were scored.

Each student was observed four times per minute. Interobserver agreement checks were completed on 15 percent of the ratings.

Phenytoin/serum level checks and EEG assessments were conducted at baseline and at points of medication reduction throughout the study, correlating these with performance ratings on the matching-to-sample task for all three subjects and on the workshop task for D and L. All three subjects were monitored for seizure activity in both their residential setting and in the workshop. Double-blind procedures were in force; ward staff, workshop staff, and subjects were uninformed if medication or placebo was in use.

The authors reported that, even at dosages considerably lower than the recommended therapeutic level, phenytoin can impair the matching-to-sample and workshop performance of mentally retarded people. The highest percentage of correct responses on the matching-to-sample task and the greatest number of assemblies completed with the lowest number of prompts occurred for each subject only after the phenytoin dose level had been reduced to 0 mg.

The authors acknowledge that the sample size severely limits the generalizability of the findings, and they recognize that the sample may be unique because of the seizure-free status of the subjects. However, they cite Davis, Cullari and Breuning (1982) in which it is estimated that approximately 31 percent of the 40-45 percent of the mentally retarded receiving phenytoin have no documented history of seizure activity. The authors conclude that it is "not unreasonable to generalize the findings to these individuals nor to suggest that many of them are experiencing an unnecessary drug-induced impairment in performance."

Panel comments: This article is based on Ms. Davis' Master's thesis. While Dr. Poling, who supervised her graduate work, did not see the subjects being tested, he told Panel members that he designed this study and that he did see the subjects, the apparatus, the data, and the consent forms. He said that the Western Michigan University Human Subjects Committee had reviewed the study. The third author, Dr. Wysocki, said that he had helped set up equipment for the study.

Through these interviews and a site visit to Coldwater, Panel members confirmed that matching-to-sample tests were carried out. A site visit to the Evergreen School adjacent to Coldwater confirmed that staff there had recorded workshop performance (Bendix bicycle brake assembly) using a form and that Ms. Davis and Dr. Breuning had access to school records. Ms. Davis told the Panel that school records were copied.

However, the article raises questions about drug manipulation. Coldwater officials maintained that drugs could not be manipulated for research purposes nor were placebos used there. This was confirmed by Dr. Wysocki who said that either the manuscript he had seen of the article did not mention placebos or double-blind procedures or he was in error for not questioning it. In any case, it was clear in his mind that placebos were not to be used with residents at Coldwater. In his interview with the Panel, Dr. Breuning commented on the use of placebos at Coldwater, indicating that placebos had been used without authorization and, early on, without having gone through standard pharmacy procedures. He said that he thought "a giant bag of them" had been purchased through a supply house in Chicago. Ms. Davis told the Panel that medication was not manipulated and placebos not used in her study, thus directly contradicting a statement in this article on which she is first author and an identical statement in her thesis. (Ms. Davis' comments on this report are appended at L.)

Panel findings: The Panel concluded that although test and workshop performance evaluations were carried out, there are serious irregularities in the published reports.

Breuning, S.E. An Applied Dose-Response Curve of Thioridazine with the Mentally Retarded: Aggressive, Self-Stimulatory, Intellectual, and Workshop Behaviors - A Preliminary Report. Psychopharmacology Bulletin, 1982, 18:1, 57-59.

PHS grant cited: MH-32206

Authors' description and findings: Subjects were 84 nonautistic, institutionalized, mentally retarded individuals between the ages of 13 and 27, with IQs ranging between 34 and 59. The subjects were reported to have been assessed for aggressive behavior, IQ, and workshop performance which involved the assembly of 15-part coaster bicycle brakes. Informed consent was obtained for each subject.

In total, there were 14 responders and 14 nonresponders assessed for aggressive behaviors, and 16 responders and 16 nonresponders assessed for self-stimulatory behaviors. For the intellectual and workshop behaviors there were 14-14 and 15-15 responders and nonresponders, respectively. Subjects were given increasing or decreasing doses of thioridazine in nine graded doses at 2-week intervals. Doses ranged from 1.0 mg./kg. to 21.1 mg./kg., as well as a period of placebo treatment. Each dose of placebo condition was reported to be continued for 8 weeks. Observations of aggressive and self-stimulatory behavior were made at 30-minute intervals during a 24-hour period over 80 weeks of the study. Treatment was reported to have been carried out under double-blind conditions.

For the responders, a dose of 5.9 mg./kg./day was optimal for reducing aggressive behaviors, and a dose of 2.5 mg./kg./day was optimal for reducing self-stimulatory behaviors. Higher doses had little additional effect except for a loss of behavioral control, i.e., increased frequencies of target behaviors. For nonresponders, the frequencies of aggressive and of self-stimulatory behaviors showed no substantial changes at lower doses but began to worsen as thioridazine doses increased. For both responders and nonresponders, there were significant decreases in intellectual and workshop behaviors at even low doses and a continued worsening as the dose was increased. Performance in the IQ-SR+ task was substantially more sensitive to dose changes than it was in the workshop task. For all the response measures of both responders and nonresponders, identical dose effects were obtained regardless of ascending or descending order of conditions.

Relation to other studies: Breuning, Ferguson, and Cullari (1980) is cited as reference for the procedures for observations of aggressive and self-stimulatory behavior. Intellectual behaviors were assessed, using procedures described in Breuning and Davidson (1981). Workshop behaviors were assessed, using procedures described in Davis, Poling, Wysocki, and Breuning (1981), presumably part of a large study also reported in Breuning, Davis, Matson, and Ferguson (1982), and it is similar to Breuning, Ferguson, Davidson, and Poling (1983) in design and use of thioridazine, except that the latter data are reported on 40 adolescent subjects with DSM III diagnoses.

Panel comments: This is an elaborate study that would have required the collaborative efforts of numerous individuals, both in residential units and at a workshop. Physician involvement in the drug protocol would be mandatory. However, no such individuals are identified or acknowledged in the publication.

In discussing his work with neuroleptic drugs with the Panel, Dr. Breuning stated that the data reported in this study were combined from data collected at the Coldwater Regional Center and the Chicago area between 1974-1977. When questioned about the data collected in the Chicago area, Dr. Breuning was unable to cite any of the institutions by name or location or to identify individuals who were involved in conducting the study.

The Panel conducted extensive interviews with Dr. Breuning's coworkers and administrative staff at Coldwater. The Panel was unable to find anyone who had direct knowledge of a double-blind placebo-controlled study that would have lasted more than a year and a half, nor any evidence that drugs had been manipulated in a manner consistent with the protocol.

The Panel was able to ascertain that extensive workshop performance records on a bicycle brake assembly project were kept at the Evergreen School where special education services were provided to on-campus clients at the Coldwater Regional Center. The Panel interviewed Mr. Timothy Smoker, the Pre-vocational and Vocational Coordinator, Evergreen School, who stated that Dr. Breuning had access to the client records and spent considerable time abstracting data from these records. Mr. Smoker stated, however, that he was not aware that any clients were being given placebos.

Dr. Breuning told the Panel that drug orders at Coldwater were written by Dr. Carlos Budding. Dr. Budding is now in Argentina and not available for comment. Dr. Breuning said that placebos had been made up on his unit and that they did not, initially, go through the pharmacy. When questioned about matched placebos and where they were obtained, Dr. Breuning said that he thought they were bought at a supply house in Chicago. Dr. Breuning said the placebos were "similar in appearance" and said "to me, a dark colored gel capsule, one looks a lot like another one."

The Panel found no consent forms for any of the subjects at Coldwater. Dr. Breuning was unable to tell the Panel where these forms were.

Panel findings: The Panel could find no evidence that such a systematic study was ever carried out. The study, as a whole, appears to be implausible because it could not have been conducted at any known site available to Dr. Breuning over the prolonged 80-week timeframe of the reported observations. The Panel concludes that, although some data may have been abstracted from other ongoing clinical efforts, the described study was not conducted.

Breuning, S.E., Davis, V.J., Matson, J.L., and Ferguson, D.G. Effects of Thioridazine and Withdrawal Dyskinesias on Workshop Performance of Mentally Retarded Young Adults. American Journal of Psychiatry, 1982, 139:11, 1447-1454.

PHS grants cited: MH-32206 and MH-30915

Authors' description and findings: This is a two-part study of the effects of thioridazine and withdrawal dyskinesias on the workshop performance of mentally retarded young adults. In part 1, 80 institutionalized mentally retarded persons were studied, 38 female and 42 male, ages 14-26, and with IQs ranging from 19-53. They were divided into 5 groups of 16. Subjects were assigned to groups on the basis of scheduled drug trials and were observed in workshop performance on a bicycle brake assembly task over a 28-week period of drug withdrawal. Informed consent was obtained from the legally responsible parent or guardian, and each of the subjects was determined by a physical therapist and neurologist not to have any identifiable perceptual-motor deficit that might affect workshop performance.

According to medical records, 60 subjects had a DSM-III diagnosis of undersocialized, aggressive conduct disorder; 5 were diagnosed as having undersocialized, nonaggressive conduct disorder; 5 as having socialized, aggressive conduct disorder; and 10 as having undifferentiated schizophrenia. Five schedules of administration characterized the groups that were matched for age, IQ, sex distribution, duration of medication, and medication dosage. Conditions included medication throughout the study, abrupt withdrawal after 10 weeks, gradual withdrawal, institution of medication midway in the study, and no medication throughout the study. Placebos were administered to groups that were either withdrawn from medication or started on medication for part of the study period. Staff were unaware of the study and completely blind to medication charges.

Each subject attended a workshop for 30 minutes each day, 5 days a week. The workshop task was the assembly of a 15-part coaster bicycle brake. Brakes were assembled individually rather than on an assembly line.

The major finding was that thioridazine can impair the workshop performance of the mentally retarded. Greater improvement of performance during the first 10 weeks was observed in the two groups not receiving medication. The group placed on medication at 10 weeks exhibited sharp deterioration in performance in the week after administration. There was a basic trend toward improvement over the 28 weeks in all the groups, but the best performance was observed in the groups not medicated or withdrawn from drugs.

In part 2, select conditions of part 1 were replicated with additional controls for examining effects attributable to withdrawal and persistent (tardive) dyskinesias. Twenty-eight subjects from the larger sample were divided into four matched groups of seven subjects each whose thioridazine dose was abruptly or gradually discontinued and who did not did not have withdrawal dyskinesias. Part 2 subjects were 11 females and 17 males, ages

14-26, with IQs from 45-69. (There is no explanation of the discrepancy in IQ range between Parts 1 and 2 (Part 1 is 19-53, Part 2 is 45-69, yet the Part 2 sample is said to have been drawn from Part 1.)

Subjects were assigned to the four groups using the matching criteria described in Part 1. Assessments of dyskinesia and withdrawal symptoms (both before and throughout the present study) were made 3 days before the onset of thioridazine discontinuation and at 1-week intervals following the start of discontinuation. Weekly assessments continued throughout the study at 1-week intervals. The Withdrawal Emergent Symptom Checklist (WESC) was the primary assessment device and was administered by two registered nurses.

Each subject attended the workshop for 45 minutes each day, 5 days a week. The workshop task was the assembly of a mock camswitch actuator. Each actuator was assembled individually, with a total of 74 steps for completion. Three response measures were taken. These steps were completed per hour, percentage of norm, and wage.

Reported findings for part 2 were that workshop performance declined with the onset of the dyskinesias and improved as the dyskinesias subsided.

Relation to other studies: Workshop behaviors were assessed using the procedures described in detail in Davis, Poling, Wysocki, and Breuning (1981). It is presumably part of a larger study also reported in Breuning (1982).

Panel comments: This is a large and complex study with an extraordinary sample of five almost precisely matched groups. The study would have to have been carried out some time after the availability of the DSM-III mentioned in the article. The 28-week study and the followup (Part 2) to look at dyskinesias would have taken over a year to complete. The article was received for publication in April 1981. Thus, the study would have begun in 1980. This would have required the study to have been done at Coldwater.

In discussions with staff and coworkers at Coldwater, the Panel could find no evidence that a study with this type of medication design had been carried out there. When questioned about the reference to the DSM-III in this paper, Dr. Davidson stated that the ICD-9 had been used at Coldwater.

When questioned about her role in this study, coauthor Vicky Davis stated that she had not been involved in the data collection, only in the writing. Ms. Davis said that she had not asked to see the raw data for the study. Ms. Davis would not comment when questioned about the use of placebos at Coldwater or about Dr. Breuning's work using thioridazine.

In discussing his role as coauthor in this study, Dr. Ferguson stated that he had not known he was a coauthor until later and that he had only been involved in the discussions of the graphs. Dr. Ferguson stated that he had not seen any raw data for the study.

In an interview with the Panel, coauthor Dr. Johnny Matson stated that Dr. Breuning said he had a large set of data and wanted to consult with him on the statistical aspects. In a written statement to the Panel, Dr. Matson stated that his role in this study was to consult on the methodological issues and to assist in the writing of the manuscript, which occurred at the University of Pittsburgh after the data in question had supposedly been collected at Coldwater. Dr. Matson further stated that he had never seen raw data, consent forms, or any other evidence that the information in question had been collected as reported.

When asked by the Panel to identify the neurologist or physical therapist mentioned in this study, Dr. Breuning said he had not meant to imply that such assessments were part of the data collection; rather, "There was an assessment by those people not identifying them as having these kinds of problems." When asked where the study had been conducted, Dr. Breuning stated that this study involved a combination of two places, Coldwater and the Chicago area where work was carried out during the mid-1970s. When questioned about the consent forms, Dr. Breuning stated that he assumed the forms were kept at the facilities. Dr. Breuning could neither identify a specific site in Chicago where the data may have been collected nor give the names of the investigators carrying out the work.

Panel findings: No studies with this kind of medication design were approved or known to have been carried out at Coldwater. The Panel found improbable Dr. Breuning's statement that part of this work was carried out in a number of institutions in the Chicago area in the mid-1970s by investigators whose names he could not recall. The Panel concludes that the described study was not carried out.

Breuning, S.E., Sisson, L.A., Fultz, S.A., Marshall, T., and Bregman, J.D. Effects of Neuroleptic Drugs on Titrating Delayed Matching-to-Sample Performance of Mentally Retarded Children. Submitted to Psychopharmacology, unpublished.

PHS grants cited: MH-32206 and MH-30915

Authors' description and findings: This paper reports on a study of the effects of neuroleptic drugs on the response performance of 12 institutionalized mentally retarded children. Subjects were five females/seven males, ages 7.5 to 12.6 years, with IQs from 55-67. Inclusion criteria were: mental retardation of unknown etiology with no other neurological disorders, a history of high rates of aggressive behavior which had been reduced by no more than 60 percent after 3 weeks of behavioral treatment, a psychiatric diagnosis of Undersocialized Conduct Disorder, and a history of no neuroleptic medications. Parental consent was obtained.

Staff and subjects were blind to conditions. Medications and placebos were administered at 8:00 a.m. and 8:00 p.m. daily in identical capsules. Medications (chlorpromazine, thioridazine, and haloperidol) were randomly assigned. Subjects received each drug in the same sequence: placebo, dose 1 (1.5 mg./kg./day), dose 2 (3.0 mg./kg./day), dose 3 (4.5 mg./kg./day), dose 2, dose 1, placebo.

On the day of admission and once or twice weekly thereafter, each participant was reported to have received a standardized battery of tests (not identified) rating the occurrence and severity of side-effects and abnormal movements. According to Ferguson and Breuning (1982), particular attention was given to extrapyramidal effects and dyskinesias. No subjects experienced adverse reactions.

The experimental room and apparatus are described in detail. Each subject received three preexperimental sessions of 15 minutes duration each to train them in a zero-delay, matching-to-sample task. The sessions were conducted at the same time each day for each participant, 60 minutes before lunch or 120 minutes after lunch. It was reported that all participants were able to respond independently at 90 percent or better by session 5. In the experimental study, matching-to-sample sessions were conducted three times weekly with 1 or 2 days separating sessions. Each session consisted of 30 trials. Titrating delay procedures were initiated once the session was underway; the delay occurred between the depression of the center response window and the illumination of the comparison stimuli.

The titration schedule consistently varied the length of the delay interval. Sessions began with a zero delay. Following the first correct response, the delay interval was increased to 1 second for the subsequent trial and thereafter through an incremental progression up to 90 seconds. An incorrect response would cause the delay to decrease to the next lowest value, and it would be increased again only after four correct responses had occurred.

Limit of delay, the longest delay value at which the subject produced a correct response within any given session, was the primary dependent variable.

Findings were presented in terms of drug responders and nonresponders for each of the medications. Responders were defined as those subjects whose rates of aggressive behavior were reduced by a mean of at least 50 percent across the last week on one of the three doses of a given medication. Nonresponders were defined as subjects who displayed no functional increase or decrease in aggressive behavior. The authors reported that each subject achieved a substantial limit of delay during the initial placebo phase and that each subject demonstrated a decrease in performance at the initiation of medication. Dose-dependent effects were observed with each medication. The reported findings uniformly demonstrated that the highest level of performance was achieved when subjects received no drugs and that the poorest performance was achieved at the highest drug dose levels. Those subjects receiving chlorpromazine or thioridazine were described as showing similar performance responses to the medications, regardless of whether or not a therapeutic effect was gained. It was stated that, for those receiving haloperidol, the therapeutic responders displayed less behavioral impairment at the lower dose levels than did nonresponders. Both responders and nonresponders were said to have demonstrated similar levels of impairment at the highest dose level.

The authors state that the findings are of importance for several reasons. They confirm the sensitivity of the matching-to-sample procedures in assessing drug effects with the mentally retarded. It was stated the findings also replicated those of Wysocki et al (1981) regarding the dose-dependent suppression effects of thioridazine on delayed MTS performance of mentally retarded young adults, and these findings extended to a pediatric population, using both prospective and withdrawal evaluations. Finally, the findings are noted as identifying the dose-dependent suppression effects of two other neuroleptic drugs: thioridazine (this apparently should have been listed as chlorpromazine since the dose-dependent suppression effects of thioridazine were reported in Wysocki et al., and haloperidol.

The authors suggest several biochemical explanations for the effects observed. Other factors were suggested as possibly being involved; subject history, for example, when coupled with possible interaction differences with the medications, could account for differences in the results. Emphasis should be placed on the accurate reporting of medication status in studies involving the mentally retarded, and the authors note that this information is generally not reported in such studies. Its absence raises questions about the generalizability of research findings among this population.

Relation to other studies: As noted in the reported description, this study is similar to Wysocki et al. (1981) in which essentially the same findings regarding medication effects are reported.

Panel comments: The list of coauthors and the address for reprint requests would indicate that this study was conducted on the Merck Unit at the University of Pittsburgh. In response to a letter from the Panel, Dr. Breuning stated that the study was conducted at Coldwater and at Pittsburgh. The same problems pertain to this study as to the others supposedly conducted on the Merck Unit. As reported by the University of Pittsburgh Ad Hoc Committee, consent forms were not found, though the article states that informed consent was gained for participants. The Ad Hoc Committee's review of pharmacy and admission records during the period of Dr. Breuning's tenure indicated that patients of the ages and diagnoses described were not available on the Unit. While coauthors Sisson and Fultz confirmed that matching-to-sample sessions were conducted daily and subjects usually had sessions three times weekly, they told the Panel that sessions were not scheduled as called for in this study and neither observed the dramatic effects reported here.

Panel interviews at Coldwater confirmed the use of matching-to-sample equipment there, but administrators insisted drug manipulation for research purposes was not permitted nor were placebos used there. The Panel was told that the Coldwater Research Committee did not approve protocols involving use of placebos, and no consent forms were found for this study.

Panel findings: The Panel concluded that the described study was not carried out.

Breuning, S.E., and Poling, A.D. Pharmacotherapy. In J.L. Matson and R.P. Barrett (Eds.), Psychopathology in the Mentally Retarded, New York, Grune and Stratton, 1982, 195-251.

PHS grant cited: MH-32206

Authors' description and findings: Included in this review of pharmacotherapy with the retarded, which is also analyzed under that category below, is the report of a pilot study that compared dosages of 0.3, 0.7, and 1.0 mg./kg. of a stimulant, methylphenidate, with six mentally retarded hyperactive individuals, four prepubescent children (11-13 years) and two adolescents (15 and 18); four were male and two female, equally divided among children and adolescents. Dose-response curves are presented of the methylphenidate effects on two measures: The Abbreviated Connors Teacher Rating Scale (ACTRS) was recorded daily, and a fixed-ratio (FR) responding task at three levels (FR 5, 10, and 20) was administered.

There were three randomly counterbalanced dosage sequences with two individuals per sequence. Each sequence lasted 7 days, with 7 days of placebo (double-blind) before and after. (Thus the experiment would last a minimum of 36 days, one of which was a pre-treatment baseline day.) Reported results were (1) four of the six subjects had substantially reduced ACTRS scores at 0.3 or 0.7 mg./kg. levels; (2) one showed a very slight reduction in ACTRS scores at 0.3; (3) one showed progressive increases in ACTRS scores across dosage; and (4) for five of the six, ACTRS scores were highest (above baseline and placebo) at the 1.0 mg./kg. dosage. With regard to FR performance, five of the six showed optimum performance at 0.3 mg./kg. and worsened performance across increased dosages; the one subject who had shown progressive increases in ACTRS scores showed no FR performance enhancement.

Relation to other studies: This pilot is similar in many respects to work reported in Poling and Breuning (1983) and Breuning, Ackles, and Poling, unpublished, both analyzed in Appendix J.

Panel comments: These data are remarkable for their complete consistency across measures with a clear curvilinear response shown in five of the six subjects. Given the use of a stimulant and the similarity to data reported in progress reports from the University of Pittsburgh, the reader would assume that the pilot work was carried out there. The Panel established, however, that Fixed Ratio equipment was not functional at Pittsburgh during Dr. Breuning's tenure. The Pittsburgh Ad Hoc Committee's search of pharmacy and clinical records established that subjects meeting the criteria in this pilot were not available. Coauthor Poling told the Panel that he was under the impression that the stimulant data came from Pittsburgh, but he was later told by Dr. Breuning that they came from Oakdale and Chicago. Dr. Breuning himself told the Panel that he had collected the stimulant data in Chicago area schools in the mid-1970s.

Panel findings: These pilot data show uniformity of outcome and agreement across measures that seem, at best, implausible. The study could not have been carried out at Pittsburgh, and the complex double-blind, drug-placebo crossover design and daily ratings make it impossible that the study could have been conducted in Chicago area schools. The Panel concluded that the study described was not carried out.

MULTISTATE SURVEY OF THE INSTITUTIONALIZED RETARDED

Davis, V.J., Cullari, S., and Breuning, S.E. Drug Use in Community Foster-Group Homes; in S.E. Breuning & A.D. Poling (Eds.), Drugs and Mental Retardation, Springfield, Ill., Charles C Thomas, 1982, 359-376.

PHS grant cited: MH-32206

Authors' description and findings: This study describes a very large survey of the use of medications among the mentally retarded in foster or group homes in the community. A random sample of 3,750 cases was selected from a case list of 15,000 obtained from mental health agencies in Illinois, Indiana, Michigan, and Ohio. Exclusion criteria were residence with parents, IQ within two standard deviations from the mean as measured by a norm-referenced test, or failure to meet the American Association of Mental Deficiency (AAMD) adaptive behavior criteria of mental retardation. A two-page questionnaire was completed for 3,496 of the sample, providing demographic information, prevalence and type of drug used, institutionalization history, degree of mental retardation, behavior problems, medical supervision, drug holidays, adverse response monitoring, and staff training.

The study reports that 74.3 percent of the sample were receiving one or more of ten drugs, seven of which were most commonly used in the subject population. The seven drugs most often prescribed were: thioridazine (43.3 percent), phenytoin (34.7 percent), phenobarbital (19.4 percent), chlorpromazine (15.9 percent), diazepam (6.9 percent), haloperidol (6.3 percent), and methylphenidate (2.4 percent). The lesser used drugs were primidone (1.3 percent), carbamazepine (1.1 percent), and ethasuximide (0.9 percent). Frequency and order of usage were fairly constant across the four States. Dose levels tended to be in the moderate to high range, with dosages at the upper end of the range far exceeding recommended levels. Multiple drug use was frequent, with antiepilepsy medications being most commonly combined. It was reported that 57.6 percent (2,014) of the population received an antipsychotic drug, alone or in combination with another antipsychotic medication. Thioridazine was most commonly prescribed in the community population, matching the pattern observed in institutions. A large percentage of the population (53.9 percent) received antiepilepsy medication, most in combination dosages. Phenytoin and phenobarbital were most commonly prescribed together, and phenytoin alone was the most often prescribed antiepilepsy medication.

Slightly over half of the sample (52.1 percent) had been institutionalized for other than diagnostic purposes for a period longer than 45 consecutive days. Special attention was called to the fact that 62.5 percent of those who had been institutionalized were receiving no medication. This was seen as contrary to the usual expectation of greater drug use among the subsample of those who had been institutionalized.

The comparison of the institutionalized-noninstitutionalized subgroups disclosed similarities to the findings of other investigators in studies comparing drug use among institutionalized subjects and those in public schools. Thioridazine tended to be the drug of choice for the institutionalized, whereas methylphenidate was prescribed more frequently for the public school population. The same finding was reported in this study, with the further similarity that behavior which was seen as psychotic among the institutionalized was called hyperactive in those without institutional histories.

Comparisons were made between drug use and degrees of mental retardation. Of the 3,496 subjects, 47 percent were mildly retarded, 29 percent were moderately retarded, 18 percent were severely retarded, and 6 percent were profoundly retarded. Among these groups, the moderately retarded were least likely to be medicated. Forty-four percent of the moderately retarded, as compared to 17.9 percent of the mildly retarded, 21.1 percent of the severely retarded, and 11.5 percent of the profoundly retarded, received no medications. Thioridazine was most often prescribed for the mildly retarded, decreasing across functioning levels. Similar trends were noted for the other behavior control medications. An opposite effect was observed for the antiepilepsy drugs. This was explained by the greater control problems among the mildly retarded and the more frequent seizure disorders among the profoundly retarded.

Age and sex were found to have little correlation with medication prescription. The only finding of significance was that mentally retarded males between the ages of 5 and 16 were much more likely to receive methylphenidate. This finding was attributed to the fact that this group is more frequently diagnosed as Attention Deficit Disorder with Hyperactivity.

The article reported on the monitoring of drug use. Both direct care and professional staff were surveyed. Attention was focused on four issues: operational definitions of behaviors justifying psychotropic drug use; regular medical supervision; scheduled drug-free periods; and monitoring of adverse reactions and side effects.

The article reported serious deficits in all these areas. Operational definitions of target behaviors were found for only 109 individuals (5.4 percent) of the 2,014 receiving antipsychotic drugs. Hyperactive behavior was defined for only 3.5 percent of the 86 subjects receiving methylphenidate. Otherwise, behavior was defined on the basis of global listings of problem behaviors. These reports were interpreted about half the time in conjunction with staff and about half the time by the prescribing physician alone.

The authors reported that frequently no documentation was provided as to why a medication was prescribed. There was no documentation for 440 (21 percent) of the 2,098 subjects receiving psychotropic medications, though there was no evidence of these patients being difficult to manage. Moreover, it was reported that 81 percent (357) of these 440 subjects had entered the community living arrangement on no drugs and had had medications prescribed on the basis of the physicians' belief that drugs were "good for the mentally retarded."

Of the 1,623 subjects receiving antiepilepsy medications, 78 percent (1,265) had documented EEG abnormalities, and 69 percent (1,119) had records of observed clinical seizures. This begs the question of the basis for medicating those who had no documentation of abnormal EEG and no record of seizure activity. An investigation was reported to have disclosed that 301 subjects (18.5 percent) had neither documentation of EEG abnormality nor records of clinical seizures. Further investigation demonstrated that 72 of these subjects were reciving an antiepilepsy medication in an effort to manage inappropriate behavior. Effectiveness was not recorded, though the mean length of chronic use of antiepileptic drugs in this fashion was 1.2 years. It was reported that no rationale could be found for the use of these medications with the remaining 229 subjects for whom no objective symptoms were reported. The mean length of chronic use was 1.7 years.

The article stated that there was no continuous medical supervision of drug use for any of the areas surveyed, except for one county in Michigan and one county in Illinois. The counties in Illinois and Michigan where physician review was carried out on a monthly basis represented 9 percent (206) of the 2,098 subjects who were receiving medications. It was reported that medication review documents for the other regions were typically signed by the physician after being prepared by a nurse or some other physician representative. Eight-hundred and eighteen (39 percent) of the 2,098 subjects receiving psychotropic drugs were reported not to have been seen even by the prescribing physician's representative.

The article cited some improvement in the coverage of antiepilepsy medications. Only 260 (16 percent) of the 1,623 subjects were not seen at least once monthly by the prescribing physician's representative. It was reported that only 6 percent of the subjects receiving antipsychotic drugs had a consulting psychiatrist, while 38 percent of those receiving methylphenidate had a consulting pediatrician, and 47 percent of those receiving an antiepilepsy medication had a consulting neurologist.

Drug-free periods were rare: Only 76 (4 percent of 2,098) subjects among those receiving a drug had a scheduled drug holiday. All 76 were reported to be receiving only one drug, and of that number 29 received methylphenidate, and 47 received one of the antipsychotic drugs.

Adverse reactions were systematically monitored by means of a 15-item reaction checklist completed weekly for 251 (12 percent) of the 2,098 subjects receiving psychotropic drugs. They all were reported to be the patients of the same physician. For 59 percent of the study population, staff were directed to inform a professional staff person of any adverse reactions to medications. They were not told, however, what constituted an adverse reaction. There was no evidence of any adverse reaction monitoring of the remaining 29 percent of the subjects.

The reported level of staff training reflected the general inattention to drug usage noted in the article. Only 47 (9 percent of the 526) home operators had received a training program, with a combined total of more than 2 hours, covering even basic details of drug usage.

The authors concluded that drug use in community placements is as prevalent as in institutions. They argued that the belief that community placement would reduce drug use was unfounded. On the contrary, the patterns of use were much the same as in institutions. Drugs were only sparsely monitored, and staff were not trained in all the factors relating to drug use.

The authors argued that drugs are overused among the noninstitutionalized mentally retarded. Evidence to support efficacy is lacking, and the monitoring of medication reactions is inadequate, as is training for the assessment of need of medications.

The authors offered a 10-point guideline for the use of drugs with the mentally retarded. They concluded, however, that little improvement will occur unless the aggrieved are prepared to file suit as a means of bringing about changes.

Relation to other studies: This study is a survey report which is not substantively related to any of the other studies reviewed by the Panel.

Panel comments: The first author of this chapter, Vicky J. Davis, when interviewed by the Panel, said that she had prepared a portion of the introduction based on her possession of copies of the referenced studies, that her basic role was one of "looking at information on movement in and out of the facility," and that her part "was the Coldwater data." She indicated that she had reviewed the records of the Social Services Department at Coldwater from which she obtained case numbers and names and was "able to see if they were on medication," and that she "went through the data for birthdates and weights." She said that she had seen a copy of the questionnaire but, when asked if she had seen the filled-out questionnaires, said that she had not. She could not say who collected the data or how they were collected, how the study was funded, or where or how the data were analyzed.

Ms. Davis said that Dr. Breuning had conducted the study and that he had placed her name on it as first author. She said that he had made the contacts with people at the State level, arranged for the data collection, and analyzed and kept the data. She said she believed the study had been carried out, although there were no records and she had seen no data other than in summary form.

The second author, Dr. Cullari, told the Panel that the original idea for the study had been his but that all the contacts for data collection were made by Dr. Breuning who had done all the data analysis. Dr. Cullari said that he had participated in preparation of the introduction, but the rest of the article had been written by Dr. Breuning. He never saw raw data, and he was uncertain if he had ever seen the questionnaire. Dr. Cullari said he thought that Dr. Breuning had conducted part of the study but maybe had made up the rest.

As described, this project would have required a large investment of time on the part of a number of people in the community. In his interview with the Panel, Dr. Breuning said that data had been gathered from local mental health boards and that Mr. Fred Morris, Calhoun County, Michigan, was the one name he could recall of those who had arranged for data to be sent to him. When Mr. Morris was contacted by telephone, he remembered having Dr. Breuning speak at a seminar but denied that he had ever been involved in any research with him. He said he had not helped gather data. In the article, Mr. Morris is named as one of the people who provided training for the managers of foster homes in which patients were placed in the community. Mr. Morris said that he never had such a role. He said that, as part of his responsibility as the Director of the Calhoun County Mental Health Center, he had worked with a few foster home owners at their request, advising them about the use of psychotropic drugs with the mentally ill. He said there may have been a few developmentally disabled persons in the homes of those with whom he met, but that fact was entirely peripheral to the reason for the meeting. In brief, Mr. Morris failed to support Dr. Breuning's contention that he had facilitated any part of the survey reported in this article.

Reducing and entering the data for computer analysis would have been a huge and time-consuming task. The questionnaire alone would have been 6,992 pages of information. It was impossible to determine the number of data items, since Dr. Breuning did not provide the Panel with a copy of the questionnaire, and yet Dr. Breuning said he had personally punched in most of the data on computers at Western Michigan University. Dr. Cullari said he had his own computer account at Western Michigan and Dr. Breuning had used it on occasion for small pieces of work only and not for work of the proportions necessary for the amount of data reported in the article. A check of the records of the Computer Center by the Chairman of the Department of Psychology failed to produce a record of Dr. Breuning's having used the center. Dr. Cullari said he thought the computer work had been done at the University of Illinois, but Panel staff confirmed that Dr. Breuning had not had access to the computers at the University of Illinois and that the computer work necessary for this article had not been done there.

At his meeting with Panel members in November 1985, Dr. Breuning said he was not sure whether or not he might still have copies of the questionnaire. He said that generally he did not keep data beyond 6-12 months. When asked if he thought it odd that no one else had seen the data for a study of this size, Dr. Breuning said that he did not. When asked why only he handled the data for such a large study, he said that he enjoyed doing it recreationally.

Panel findings: The Panel could find no confirmation that this large study was carried out. Neither the first nor the other coauthor ever saw primary data, nor did they have any idea how such a large study was paid for. Both stated independently that they were involved in preparing only the introductory portions of the work or, on Ms. Davis' part, providing limited data from only one location, Coldwater, and that Dr. Breuning had arranged for data collection and analysis and had done most of the writing. Dr. Breuning was able to provide the name of only one person who was said to have participated in the project, and that person denied any knowledge of the study. Dr. Breuning's account of where the computer work for data analysis was done was not substantiated. These factors brought the Panel to the conclusion that the study described was not carried out.

REVIEWS

Breuning, S.E. and Poling, A.D. Pharmacotherapy. In J.L. Matson and R.P. Barrett (Eds.), Psychopathology in the Mentally Retarded, New York, Grune and Stratton, 1982, 195-251.

PHS grant cited: MH-32206

Description: (A pilot study reported in this article is analyzed under Studies on Therapeutic Manipulation of Task Performance, above.) This article provides an overview of pharmacotherapy with the retarded. Included are a brief historical review and sections on drug classification, rationale for pharmacotherapy (by drug classes), prevalence of drug use, pharmacology, therapeutic use and side effects, methodologic issues in assessing drug effects, efficacy of drug and behavioral alternatives, and litigation issues.

Many of the studies reviewed by the Panel are cited, frequently either to bolster the argument for greater methodological rigor in research on pharmacotherapy with the mentally retarded, i.e., Breuning, Ferguson, and Cullari (1980) demonstrating the importance of placebo-double-blind procedures, or to bolster the authors' views on neuroleptic treatment. Breuning (1982) is cited (along with a conference, presentation, and unpublished work by Dr. Breuning) to illustrate the authors' suggestion that fewer than 15 percent of the mentally retarded receiving neuroleptics show decreases in target symptoms.

The article concludes that neuroleptics are greatly overused with the mentally retarded, that their use is most likely to decrease learning and performance, that they often produce contratherapeutic changes in target behaviors, and that they have an "incredibly low" risk-to-benefit ratio. The article calls for methodologically rigorous investigations of antiolytics, antidepressants, antimanics, and stimulants. It notes the inexpensiveness and increased ease of patient management with limited staff of drug therapy, and applauds court decisions requiring documentation of the value of such therapy.

Panel findings: This review article relies heavily on work by Dr. Breuning that the Panel concluded was not carried out as described. It, therefore, must be regarded as scientifically unsound and misleading.

Ferguson, D.G. and Breuning, S.E. Antipsychotic and Antianxiety Drugs. In S.E. Breuning and A.D. Poling (Eds.), Drugs and Mental Retardation. Springfield, Ill., Charles C Thomas, 1982, 168-214.

PHS grant cited: MH-32206

Description: This is a review article largely focused on use of antipsychotic drugs with the mentally retarded. For this category of drugs, it includes sections on pharmacological properties, physiological effects, therapeutic use, short- and long-term side effects, behavioral effects and their assessment, and efficacy. It gives special attention to the phenothiazines.

The article presents findings from studies reviewed by the Panel, particularly those on behavioral effects and their assessment, efficacy, and behavioral alternatives to or combination with drug management of behavior. These studies are presented as methodological improvements. The efficacy of drug treatment is questioned, and behavioral alternatives are urged. The relatively slight literature on anti-anxiety drugs is reviewed with attention to the same kinds of issues as for antipsychotic drugs. The paucity of research on these drugs is deplored, and a larger research data base on both categories of drugs is called for. Breuning, O'Neill, and Ferguson (1980) and Wysocki, Fuqua, Davis, and Breuning (1981) are cited as methodologically strong studies of nonresponders to drugs, and Breuning, Ferguson, Davidson, and Poling (1983) as studies of responders and nonresponders.

Panel findings: The section of this article on anti-anxiety drugs appears well-done. The section on antipsychotic drugs relies heavily on studies by Dr. Breuning that the Panel concluded were not carried out as described. This part of the article must be regarded as scientifically unsound and misleading.

Breuning, S.E., Davis, V.J., and Poling, A.D. Pharmacotherapy with Mentally Retarded: Implications for Clinical Psychologists. Clinical Psychology Review, 1982, 2, 79-114.

PHS grant cited: MH-32206

Description: This review article describes and discusses six classes of psychotropic drugs frequently used with the mentally retarded, the therapeutic and countertherapeutic effects, alternative treatments, and other issues involving limitation of and legislation of drug use with the mentally retarded. The intent of the article is to provide background for clinical psychologists in working with the mentally retarded.

The article raises questions about the extent of drug use with the mentally retarded. It represents the prescription of these medications for the mentally retarded as being based mainly on experience with the mentally ill. It declares that efficacy can be demonstrated in fewer instances than the rate of medication use suggests, argues that medication dosages in the lower ranges have been shown to have greater beneficial effects than in the higher ranges, and states that behavioral techniques have been shown to be more effective than medications in improving and controlling the functioning of the mentally retarded. Many of Dr. Breuning's studies are cited.

Panel findings: Many of the findings reported here are from studies which the Panel has concluded were carried out as described. The paper must thus be regarded as scientifically unsound and misleading.

Barrett, R.P. and Breuning, S.E. Assessment of Intelligence, in J.L. Matson and S.E. Breuning (Eds.), Assessing the Mentally Retarded, New York, Grune & Stratton, 1984.

PHS grants cited: MH-32206, MH-30915, and MH-37449

Description: This chapter reviews the intelligence tests often used and referred to in evaluating the mentally retarded. It covers the development of intelligence tests in general and the strengths and weaknesses of the more frequently used tests. No data were collected for the preparation of this material, and conjectural comments are limited. The brief section on medication effects cites findings from Breuning and Davidson (1981), Breuning, Ferguson, and Poling (1983), and Breuning (1982), all on effects of medication on IQ, but refers to the findings as tentative. The reader is referred to Sisson and Breuning (1984) and Breuning, Davis, and Poling (1982).

Panel findings: With the exception of one section, this appears to be a straightforward review of available instruments. The section on medication effects, however, depends on studies which the Panel has found to be not carried out as described. Even though labeled tentative, these findings are seriously misleading.

Sisson, L.A. and Breuning, S.E. Assessing Medication Effects, in J.L. Matson and S.E. Breuning (Eds.), Assessing the Mentally Retarded, N.Y., Grune and Stratton, 1984.

PHS grants cited: MH-32206, MH-30915, MH-37449.

Description: This chapter reviews the history of the use of psychotropic drugs with the mentally retarded and discusses ethical and legal reasons for rigorous assessment standards, focusing in some detail on major litigation resulting in court orders involving pharmacotherapy. It then reviews the literature on such aspects of assessment as measures of target behaviors, learning and performance measures, behavioral observations, measurement of side effects, dyskinesias and withdrawal effects, and assessment design. The chapter relies heavily on published work by Dr. Breuning and his coauthors.

Panel comment: Coauthor Sisson told the Panel that her role in writing this chapter was in preparing a draft which Dr. Breuning rewrote extensively. She said Dr. Breuning supplied the graphs and prepared examples. She described the intent of the paper as being a review of the literature and Dr. Breuning's papers. She told the Panel that she had asked Dr. Breuning to remove her name from any papers submitted for publication.

Panel findings: This chapter extends the influence of studies the Panel has found to have not been carried out as described. It must be considered unsound scientifically and seriously misleading.

APPENDIX J
ANALYSES OF STUDIES REPORTED UNDER MH-37449

STIMULANT DRUG USE WITH MENTALLY RETARDED CHILDREN: STUDIES REPORTED UNDER MH-37449, UNIVERSITY OF PITTSBURGH

Application: Application MH/HD 37449-01, "Stimulant Drug Use with Mentally Retarded Children," from the University of Pittsburgh, with Dr. Breuning as Principal Investigator, was received at NIMH on October 1, 1981. Dr. Breuning described the proposed research as examining appropriate dose levels of stimulant drugs for use in the treatment of hyperactive, mentally retarded children. The design called for 48 mentally retarded subjects, diagnosed by DSM-III criteria as Attention Deficit Disorder (ADD) with Hyperactivity and with mild to moderate mental retardation. Subjects would have a score of 15 or higher on the Abbreviated Conners Teachers Rating Scale (ACTRS). Behavior, laboratory, and academic comparisons would be made for the 24 subjects, ages 6-12, on methylphenidate doses of 0.3, 0.5, and 0.7 mg./kg., and for the 24 subjects ages 3-6 on dextroamphetamine doses of .15, .25, and .35 mg./kg. Comparisons would be double-blind, placebo-controlled, and randomly counter-balanced. There would be an initial no-drug phase to establish baseline readings. Dosage levels would be administered over a 7-day period, each level followed by a 7-day placebo phase. Hyperactivity would be assessed by use of a recognized rating scale, direct observation by trained observers, and assessments of academic and laboratory performance. Provisions were included to insure interrater reliability. Standard statistical techniques would be employed for data analysis.

Patient flow in the John Merck Program for Multiply Handicapped Children at the Western Psychiatric Institute and Clinic (WPIC) was described as adequate to guarantee a sufficient number of subjects.

Dr. Breuning was listed as Principal Investigator devoting 20 percent effort, with 15 percent salary support requested. His responsibilities were described as being responsible for the overall coordination and administration of the project, including supervision of project staff; monitoring the assessment and treatment phases of the study; overseeing the data analysis; and preparing all resulting reports and manuscripts.

The study was planned to begin on July 1, 1982. A 24-month timetable was given, describing the plan of work, the organization and training of staff, identification and assessment of subjects, data analysis, followup assessments, and manuscript preparation. Assessments were to be conducted daily across each experimental condition, including all dependent measures on subjects admitted to the study on a staggered entry schedule. Followup data were to be collected at 3- and 6-month intervals following active treatment.

Plans for obtaining informed consent and for the protection of human subject well-being and confidentiality were made, and a risk/benefit ratio was presented. These procedures were reviewed and approved by the Institutional Review Board (Biological) of the University of Pittsburgh on January 19, 1982.

After review and recommendations for approval by an NIMH initial review group and the National Advisory Mental Health Council, an award was made for a 2-year period beginning July 1, 1982.

Progress report on the first grant year: In the first progress report, dated April 29, 1983, Dr. Breuning stated:

> Studies are proceeding nicely with respect to each of the specific aims. During the first year of this grant progress has been about as expected. Just over 65% of the children required for the methylphenidate studies have completed the protocol. Approximately 35% of the children required for the dextroamphetamine studies have completed the protocol. No problems are anticipated during the second year of the project.

The results of three studies were described. Study 1 examined the effects of methylphenidate on the fixed-ratio (FR) performance of mentally retarded children. The effects of three doses of methylphenidate, 0.3, 0.7, and 1.0 mg./kg., on the lever-pressing response performance of 12 mentally retarded children maintained under FR 5, 10, and 20 schedules of food delivery were studied. For five subjects, the prescribed doses produced decreases in response rates. For the other seven subjects, the two lower doses of 0.3 and 0.7 mg./kg. produced increased response rates, while the 1.0 mg./kg. dose decreased responding. It was reported that subjects whose FR response rates were increased by methylphenidate also demonstrated a therapeutic response to the drug, as measured by changes on CTRS scores. This study was reported in the Poling and Breuning (1985), discussed below.

The second study examined the effects of methylphenidate with hyperactive mentally retarded children ages 6-12, eight males and five females, mean IQ 52.28 and mean age 8.95. Accuracy and speed of performance were dependent variables on a discrimination task. Abbreviated CTRS and time on-task assessments were to be completed daily across conditions, and performance and accuracy measured using a titrating delayed matching-to-sample (MTS) discrimination task. Randomly determined dose levels of 0.3, 0.5, 0.7, and 1.0 mg./kg. were administered. Each dose level was separated by a placebo phase, with medication and placebo phases each lasting 7 days. Double-blind conditions for each phase were maintained for both subjects and staff. Optimal effects, as measured by reduced levels of hyperactivity, increased time on-task, and improved discrimination task performance for eight responders, were generally obtained at the 0.3 mg./kg. dose level. The five nonresponders were reported as showing little change on any measure, except that their performance on all measures deteriorated at the 1.0 mg./kg. dose level.

The third study reported on the effects of dextroamphetamine on hyperactive mentally retarded subjects, ages 3 and 6. Seven subjects, five males and two females, are listed, but data are provided for only six subjects. Mean IQ was 58.16, mean age 4.96. Response measures and counterbalancing of conditions were similar to those in Study 2. Doses of 0.15, 0.25, and 0.35 mg./kg. produced similar results. The two responders were reported as showing positive gains on all measures, while the four nonresponders showed gains on none.

Three articles were reported as written during this phase of the study:

> Poling, A.D. and Breuning, S.E. Effects of methylphenidate on the fixed-ratio performance of mentally retarded children. Pharmacology, Biochemistry, and Behavior, in press. (This article was published July 3, 1985, and is discussed below.)
>
> Sisson, L.A. and Breuning, S.E. Assessing medication effects. In J.L. Matson and S.E. Breuning (Eds.), Assessing the Mentally Retarded. New York: Grune and Stratton, in press. (This review chapter was published in 1984, and is discussed in Appendix I.)
>
> Davis, V.J., McGonigle, K., and Breuning, S.E. Effects of methylphenidate on titrating delayed matching-to-sample performance of hyperactive mentally retarded children. Submitted for publication.

Plans for the coming year were listed as the continuation of the three studies described above.

Second progress report: The second progress report was submitted as part of an application for continued support, 2 R01 MH-37449-03. It was received at NIMH on October 1, 1984. It covered activities through September 1, 1983. Fourteen staff were listed. Dr. Breuning described the original aims of the project as having been met or shortly to be met. He stated that, "During the 14 months of the project we have completed six studies and are about 65% through a seventh study."

Description of studies: The second progress report described the following seven studies:

Study 1. Poling, A. and Breuning, S.E. Effects of methylphenidate on the fixed ratio performance of mentally retarded children. Pharmacology, Biochemistry and Behavior, 1983, 18:541-4.

Subjects were 12 hospitalized mentally retarded (mean IQ 48, range 25-63) children (mean age 10.2, range 6.8-14.3), seven boys and five girls, selected on the basis of having mental retardation of unknown etiology, no other neurological disorders, and scoring above 15 on the CTRS. Parental consent to participate was obtained for each. Testing was conducted in a room 4 m. wide, 5 m. long, 2.5 m. high, equipped with a chair in which the participant sat facing a table which was equipped with a metal response lever projected outward 10.2 cm. and a food dispenser. Solid-state and electro-mechanical equipment in an adjacent room recorded responses and arranged food deliveries.

Each subject was trained (verbal instruction, modeling, and physical guidance if necessary) in a 30-minute session from a FR 1 Schedule until all participants consistently earned food at a FR 20 schedule.

The effects of methylphenidate (Ritalin) on lever-pressing under FR 5, 10, and 20 schedules of food delivery were examined. Methylphenidate (3 oral doses 0.3, 0.7, and 1.0 mg./kg.) and placebo were administered (in capsules of identical appearance) 90-100 minutes prior to the experimental session in 7-day blocks, with order of exposure counterbalanced across participants. The study was double-blind.

For five children, methylphenidate at the above doses produced generally dose-dependent decreases in response rates; for the other seven, the two lower doses increased response rates, while the higher dose decreased responding. Differential effects across participants could not be attributed to differences in control response rates or demographic factors. Each child whose rate of FR responding was increased by methylphenidate also demonstrated a therapeutic response to the drug.

Study 2. Breuning, S.E., Ackles, P.K., and Poling, A. Dose-dependent effects of methylphenidate on the fixed-ratio performance of hyperactive severely mentally retarded adolescents. Manuscript submitted to Applied Research in Mental Retardation.

Dose-dependent effects of methylphenidate on the FR performance of hyperactive severely retarded adolescents were examined. Subjects were six males, five females, age range 15-18 (mean 16.6), IQ range 21-41 (mean 30.1). Lever-pressing performances were studied during FR 5, 10, and 20 schedules of food delivery. Testing was in a room 4 m. x 5 m. x 2.5 m., equipped with a chair on which participants sat facing a table. A work panel on the table was equipped with a metal response lever that projected outward 10.2 cm., and a food dispenser that was 16.6 (range 15-18) delivered small edibles. Solid-state and electromechanical equipment located in an adjacent room recorded responses and arranged food deliveries.

Oral doses of 0.3, 0.5, 0.7, and 1.0 mg./kg. of methylphenidate were reported to produce dose-dependent decreases in response rates for five (45 percent) of the subjects; six of the subjects (55 percent) responded positively, five demonstrating an increased response rate at the 0.5 mg./kg. dose level and one at the 0.3 mg./kg. level. Ten of the eleven subjects displayed slowest response rates at the highest dose level, 1.0 mg./kg. Comparisons between FR performance and scores on the abbreviated CTRS showed a high correlation between FR 10 and FR 20 conditions and the degree of clinical response to methylphenidate, indicating that many hyperactive severely mentally retarded adolescents respond therapeutically to relatively low doses of methylphenidate.

Study 3. Breuning, S.E., Sisson, L.A., Ackles, P.K., Nuffield, E.J., Phillips, K.P., and Barrett, R.P. Multidimensional Dose-Response Curves of Methylphenidate With Hyperactive Mentally Retarded Adolescents. Manuscript in preparation.

Effects of methylphenidate with hyperactive mentally retarded adolescents, ages 14-18, were examined. Subjects were eight males and five females, with a mean IQ of 32.28 and mean age of 16.3 years. CTRS scores, time on-task, workshop, and lever-pressing assessments were completed across conditions daily. Doses of 0.3, 0.7, and 1.0 mg./kg. methylphenidate were randomly determined for each subject. Seven conditions of three doses, preceded and interspersed with placebo phases, were described. Each phase lasted 7 days. Double-blind procedures for all staff and subjects were employed for both medication and placebo conditions. Eight therapeutic responders were described as obtaining lower CTRS scores, increased time on-task, and improved performance on the lever-pressing task at an optimal dose range of 0.3 mg./kg. The five nonresponders were reported to have improved on none of the measures and to have worsened on the 1.0 mg./kg. dose.

The reported findings were interpreted as providing evidence of "dramatic improvement" on both clinical and laboratory measures among methylphenidate responders. Nonresponders displayed dose-dependent worsening on all measures. Both responders and nonresponders performed poorly at the 1.0 mg./kg. dose level.

Study 4. Breuning, S.E., Sisson, L.A., Davis, V.J., Ackles, P.K., Fultz, S.A., Duffner, P., Forster, J.L., and Barrett, R.P. Multidimensional Dose-Response Curves of Methylphenidate With Hyperactive Mentally Retarded Children. Manuscript in preparation.

This study was designed to examine the effects of methylphenidate on 6 to 12-year old hyperactive mentally retarded children. Randomly determined doses of 0.3, 0.5, and 0.7 mg./kg. were administered to 24 subjects, 17 males and 7 females, with a mean IQ of 52.28 and mean age of 9.7 years. Dependent variables were accuracy and speed of performance on a discrimination task. Time on-task assessments and abbreviated CTRS scores were completed daily across conditions. Performance and accuracy were measured using a titrating delayed MTS discrimination task. Experimenters and participants were blind to both medication and placebo. Seven phases of 7 days' duration each, interspersing placebo and dose phases, made up the experiment.

The 13 responders demonstrated improved time on-task, improved performance on discrimination tasks, and reduced levels of hyperactivity (CTRS scores), with generally optimal effects at the 0.5 mg./kg. dose level. There was relatively little change among 11 nonresponders on any of the measures except for the tendency among all to deteriorate in performance at the highest dose level.

Study 5, Davis, V.J. and Breuning, S.E. Effects of Methylphenidate on Titrating Delayed Matching-to-Sample Performance of Hyperactive Mentally Retarded Children. Manuscript in preparation.

This study examined the effects of methylphenidate on 14 hyperactive mentally retarded children with a mean IQ of 52.28 and a mean age of 8.95 years. It followed the same design as the previous methylphenidate studies. Dependent variables were speed and accuracy on a discrimination task; daily assessments across conditions using abbreviated CTRS scores and time on-task were made; and performance and accuracy were measured using a titrating MTS discrimination task. Randomly assigned dosage levels of 0.3, 0.5, 0.7, and 1.0 mg./kg. of methylphenidate were administered in four 7-day phases interspersed with five placebo phases of equal duration. Staff and subjects were blind to both medication and placebo.

The eight responders demonstrated increased time on-task, enhanced discrimination task performance, and reduced levels of hyperactivity at the optimum dose level of 0.5 mg./kg. The six nonresponders displayed little change on any measure except for the general deterioration of performance on all measures at the 1.0 mg./kg. dose level.

Study 6. Ackles, P.K. and Breuning, S.E. Effects of Dextroamphetamine on Titrating Delayed Matching-to-Sample Performance of Hyperactive Mentally Retarded Preschool Children. Manuscript in preparation.

This study examined the effects of dextroamphetamine on 12 hyperactive mentally retarded preschool children. (The report refers to both methylphenidate and dextroamphetamine as the medication used; the dosages are more reasonable for dextroamphetamine which appears to be the drug reported.) Subjects were nine males and three females with a mean IQ of 56.48 and a mean age of 4.61 years. Accuracy and speed of performance on a discrimination task were the dependent variables. Abbreviated CTRS scores and time on-task assessments were done daily across conditions. Performance and accuracy were measured by use of titrating delay MTS discrimination task. Dose levels were .15, .25, and .35 mg./kg., with randomly determined administration. The report lists "9" conditions but describes 7: three drug phases, each divided by a placebo phase and each of the phases lasting 7 days. Staff and subjects were blind to both medication and placebo phases.

The reported results were much as those of the other methylphenidate studies, except that the rate of response to detroamphetamine (33 percent) was much lower than to methylphenidate (55-60 percent). For the four responders, the general optimum dose level was .25 mg./kg. The eight nonresponders showed little change on all measures except for general deterioration of performance at the higher dose level.

Study 7. Breuning, S.E., Ackles, P.K., Sisson, L.A., Fultz, S.A., Campano, C., Forster, J.L., Nuffield, E.J., and Barrett, R.P. Multidimensional Dose-Response Curves of Dextroamphetamine With Hyperactive Mentally Retarded Preschool Children. In progress.

This study was designed as an examination of the effects of detroamphetamine on a second cohort of hyperactive mentally retarded preschool children. Thirteen subjects, nine males and four females, with a mean IQ of 58.28 and mean age of 4.7 years were reported.

The protocol followed was that of the previous studies. Speed of performance and accuracy were the dependent variables as measured on a discrimination task. Time on-task and abbreviated CTRS scores were assessment measures used daily across all conditions. Performance and accuracy were measured by use of a titrating delayed MTS discrimination task. Randomly assigned doses of .15, .25, and .35 mg./kg. dextroamphetamine were administered to each subject. The study consisted of seven conditions; three drug levels separated by placebo phases, each administered for 7 days.

Preliminary findings were much as in the previous studies. A moderate dose level of dextroamphetamine seemed to produce optimal measured results, but a far smaller number of responders than the results described in the methylphenidate studies.

For this progress report, eleven publications were listed as published, in press, or in preparation. Seven presentations were noted.

Panel assessment and comments: In his December 1983 letter to NIMH (Appendix A), Dr. Robert Sprague questioned Dr. Breuning's ability to conduct the studies reported in the time he had been at the University of Pittsburgh. In assessing the work reported by Dr. Breuning as conducted at that University, the Panel reviewed the results of the four University committees that had looked into allegations concerning Dr. Breuning and met with all of the members of the Ad Hoc Committee. It made site visits to the university and interviewed Dr. Breuning's coauthors and Dr. Breuning himself. Each event is discussed separately.

University of Pittsburgh Ad Hoc Committee

As discussed on pages 3-4, above, the three committees convened at the University of Pittsburgh in 1984 to investigate the allegations concerning Dr. Breuning's research, confining their inquiries either to work thought to have been carried out previously at the Coldwater Regional Center or to financial aspects of grant MH-37449. After a further request by NIMH, the Chairman of the Department of Psychiatry appointed, in May 1985, an Ad Hoc Committee to "determine the authenticity of data reported in the first progress report on grant MH-37449." The committee expanded its investigation to the seven studies reported in renewal application 2 R01 MH-37449-03 and described above. The committee's full report is appended at B.

Members of the Ad Hoc Committee, which was chaired by Dr. Robert E. Miller, reported that they had personally searched the individual medical records of all 278 inpatients admitted to the Merck Unit between July 1, 1980, and June 30, 1984, covering the full period of Dr. Breuning's employment at the University. The search included daily orders from physicians, medication records, and discharge summaries. If evidence of Ritalin or Dexadrine was found, records were examined for IRB consent, evidence of behavioral testing in daily progress notes, and specific discharge diagnoses. Copies of all placebo-controlled trials conducted on the Merck Unit were obtained from the WPIC pharmacy to establish which patients had received stimulant/placebo double-blind studies. The committee interviewed, personally or by telephone, several former and present Merck Unit staff. It did not interview, meet, or correspond with Dr. Breuning.

The Ad Hoc Committee's report dated May 3, 1985, concluded:

> Data from ninety-nine subjects were reported in the seven studies in the Previous Work section of the renewal application for MH37449. In our rigorous search of written records and interviews with individuals having knowledge of the research activities on the sixth floor of WPIC we were able to identify only 15 subjects who had received stimulant/placebo trials between July 1, 1981 and March 1, 1984, the period when Dr. Breuning was conducting research at WPIC. Of these 15, four appear to have received no laboratory testing of the kind reported in the Progress Reports. Eleven patients could have been research subjects although their discharge diagnoses did not fit protocol criteria in a number of instances.
>
> With regard to the 01 Progress Report dated 4/29/83, Study 1 on the effects of methylphenidate on fixed-ratio performance was not conducted at WPIC since no fixed-ratio equipment was ever employed at this site. Study 2 involved a Ritalin trial and reported 14 subjects. One patient from WPIC could have been a subject for that study and one additional subject was just beginning such a trial when the Progress Report was submitted. No other subjects could be identified for this study. Study 3 was a Dexadrine study with seven children. Three of the Merck patients were placed on a Dexadrine/placebo trial during time periods appropriate for this study but two of them did not perform the titrated delay task shown in Figure 2 of the Progress Report.
>
> The search of medical records uncovered only two signed IRB consent forms. Dr. Forster produced two more consents from her own files. Dr. Breuning's summary of research activities during the previous year filed for IRB renewal on May 17, 1983 reports a total of 21 subjects entered into the protocol. It was not possible for the Ad Hoc Committee to reconcile the discrepancies in the number of subjects or to locate the missing informed consent forms.
>
> In summary, the Ad Hoc Committee has concluded that the data for the majority of subjects reported in the 01 Progress Report, and the seven studies of the renewal application for MH37449 cannot be identified as studies conducted on the John Merck Unit of WPIC.

When the Panel met with Dr. Miller and his committee and reviewed their records, only five patients on the Merck Unit during Dr. Breuning's tenure and meeting the diagnostic criteria in the protocol were identified.

Interviews with Coauthors and Colleagues and Site Visit to University of Pittsburgh

The Panel met and corresponded with Dr. Alan Poling, first author of the published article resulting from Study 1. Dr. Poling has written the Panel that he had no role in collecting the reported data and cannot vouch for their accuracy; that he played a minor role in data analysis and research design but did not see subjects or raw data; and that he had no knowledge of how or if informed consent was obtained, nor of the physician(s) responsible for changes in medication. Dr. Poling said that at the time the article was submitted for publication, he was under the impression that at least some of the data reported were collected by Dr. Breuning at the University of Pittsburgh School of Medicine, but Dr. Breuning later stated that this was not the case. Dr. Poling also wrote to the Editor-in-Chief of Pharmacology, Biochemistry, and Behavior, in which the article appeared, that the data reported were collected by Dr. Breuning. While he had had absolute faith in their accuracy at the time the article was submitted, he could no longer personally vouch that the study was conducted as reported nor that the data were accurate. When he met with members of the Panel, Dr. Poling said that he had thought that some subjects were at Pittsburgh and some at Coldwater, but that he had recently spoken to Dr. Breuning who had told him some were from Pittsburgh and some from Oakdale. He said that Dr. Breuning assured him that he had actually done the work and had the raw data but, because of confidentiality, could not provide names of clients or dates of data collection.

Other coworkers at WPIC questioned the number of subjects reported. Dr. Patrick Ackles told the Panel that when he questioned the number of children reported as being in stimulant studies in the first progress report, he was told by Dr. Breuning that subjects were from other studies, that samples were not independent, that some data were from Coldwater, and that collaborators were getting data for him. When questions were raised about Dr. Breuning's renewal application in December 1983, Dr. Ackles said he asked to see raw data and, when Dr. Breuning could not show it to him, asked that his name be deleted from all papers. Dr. Ackles said that he was initially told by Dr. Breuning that adolescent subjects in Study 2 were from the Merck Unit before he, Ackles, had been there. Later, in 1984, Dr. Breuning told him that he had collected the data in Chicago when he was a graduate student there.

Dr. Edward J. Nuffield, formerly Acting Medical Director on the Merck Unit, and Dr. Janice Forster, staff physician on the unit for part of the relevant period, were interviewed by the Ad Hoc Committee and the Panel. Both described weekly staff meetings at which patients meeting the criteria for the stimulant study were selected. The physicians wrote the drug orders for the WPIC pharmacy and were responsible for obtaining informed consents. Dr. Nuffield could not locate copies, although he said he had kept them. Dr. Nuffield is reported to have told the Ad Hoc Committee that all children from the sixth floor (Merck Unit) given a stimulant/placebo trial were research subjects for grant MH-37449, an estimated 12-15 subjects. He is also reported by the Ad Hoc Committee to have said that not all of the subjects actually met the criteria of ADD, mild-moderate mental retardation, and hyperactivity; that, while rare, he did change diagnoses; and that neither he nor Dr. Breuning was blind to medication. However, he told the Panel that Dr. Breuning was probably blind. Dr. Forster was involved with only three subjects. Neither Dr. Nuffield nor Dr. Forster saw data from the study. Dr. Nuffield told both the Ad Hoc Committee and the Panel that, while he had become suspicious of the study because of the number of subjects being reported, he had never confronted Dr. Breuning, and that he had actually avoided such a confrontation.

Several of Dr. Breuning's coworkers were identified in application 2 R01 MH-37449-03, in roles of which they were unaware.

Dr. Patrick Ackles, listed as project staff for 10 percent effort, told the Panel that he had been a Postdoctoral Fellow on a training grant at WPIC, that his stipend was supplemented by WPIC but he didn't know the source of the supplemental funds, and that he had not spent 10-20 percent of his time on the grant. He said that he had not been asked by Dr. Breuning if he wished to be listed on the October 1, 1983, application and that, when he questioned Dr. Breuning about his name being on that application, he was told that everyone at WPIC was an investigator and staff consultant.

Ms. Sue Fultz told the Panel that she had not known she was listed as a coauthor on two reported studies (4 and 7) until after the application had been submitted. She said that she had had no role in preparing it. Similarly, Dr. Janice L. Forster, also listed as a coauthor on studies 4 and 7, told the Panel that she was unaware she was so listed.

As with studies discussed in Appendix I, coauthors did not see raw data. As noted above, Dr. Poling told the Panel that on Study 1, on which he was first author, he saw only summary data and Dr. Breuning had sent him the procedures section.

On Study 2, Dr. Ackles, the second author, told the Panel that he had drafted the paper from summary data given him by Dr. Breuning and that Dr. Breuning had rewritten and changed it. Ms. Sisson, when asked about the review paper (Appendix I) on which she was first author, said that she prepared a draft which Dr. Breuning rewrote and to which he added the graphs and examples. She also said that she had been asked by Dr. Breuning to write for inclusion in the progress report the methodology section of a FR study he said he had carried out at his previous appointment. She based this, she said, on other papers he had written.

Regarding the reported testing, both the Ad Hoc Committee and the Panel confirmed that no FR testing was done on the Merck Unit during the relevant time period. Apparently FR equipment was present in the unit at some time but was not operational. The Panel measured the room identified by Dr. Ackles as the one in which the FR equipment had been kept; it did not conform to the reported measurements.

According to Ms. Lori Sisson, Senior Research Assistant, all children on the Merck Unit who could be tested were given MTS tests, usually three times a week, but in some cases five times a week. Ms. Sisson scheduled these tests which were given by herself, Ms. Sue Ann Fultz, several nurses, and others. Ms. Sisson said she was blind to medication regimes and did not take part in research planning meetings or conferences or obtain informed consent, and so she could not identify children who were research subjects. When asked if subjects were run at specific times, Ms. Sisson said schedules were for the convenience of testing staff. Ms. Fultz told the Panel that she could recall only two children for whom testing at a specific time had been requested. According to Ms. Sisson, data were entered into records and data "strips" given directly to Dr. Breuning. Records were given to Dr. Breuning when children were discharged. Ms. Sisson said that she had plotted data daily and did not see the dramatic drug effects Dr. Breuning was reporting in his graphs.

Amended Progress Report on 2 R01 MH-37449-03 and Interview with Dr. Breuning

When Dr. Breuning met with the Panel, he gave the members an amended progress section to the renewal application. There are several major differences between the submitted and the revised reports. The original report gave detailed information regarding subjects, protocols, and medication levels for seven studies. In the original progress report, Dr. Breuning wrote:

> During the 14 months of the project we have completed six studies and are about 65% through a seventh study. One study has been published, one is in press, and manuscripts are being prepared for the other four completed studies. We are continuing with the seventh study.

In the revised version, the above is replaced by the following statement:

> During the past 14 months we have been able to analyze much previously collected data. One study has been published, one is in press, and several manuscripts are planned.

In the revised progress report, the description of Study 1 remains as it had been reported after the first grant year. The description of Study 2 remains as it was in the renewal progress report. However, Dr. Breuning noted in the revised progress report that the 11 subjects in Study 2 were also among the 13 subjects in Study 3. He indicated that data on the 0.5 mg./kg. methylphenidate dosage for these 11 subjects were dropped from the data analysis in Study 3. He further indicated in the revised version of the progress report that there was some uncertainty about how these data should be handled. Other details of the protocol and the outcome on Study 3 are as they were in the original progress report. A statement is contained in the original report that a manuscript detailing Study 3 was being prepared. That statement was removed from the revised report.

In the revised progress report, Study 4 was described as another possible way of looking at the data from Studies 1 and 2, rather than as a separate, completed study as it had been described in the original progress report, and no mention was made of Studies 5, 6, or 7. Rather, the report concludes with a statement that a number of the children who otherwise would be candidates for the studies were being effectively treated with behavioral approaches. The revision indicated that subject recruitment had become a problem for purposes of satisfying the original protocol but that other studies of interest might be conducted with the population. These possibilities were not described in detail.

Five of the eleven publications listed in the original progress report were deleted from the revised version as were three of the seven presentations originally listed.

Dr. Breuning told the Panel that no data reported in the progress section of that renewal application had been collected at the University of Pittsburgh, nor, he said, had they been collected at Coldwater or Oakdale. Rather, they had been collected in Chicago area schools, between 1974-1977, when he was a graduate student.

According to Dr. Breuning, after the grant had been awarded to Pittsburgh, he found that it was often not necessary to initiate drug treatment, that the age composition of the Merck Unit's patient population had changed, and "there was a high unlikelihood of having time to complete it." He said that the project became one of primarily gathering normative data on the "Connors Scale as well as two other scales and looking at the behavioral and time analysis of this data." When asked how many patients were actually studied at Pittsburgh, he replied:

> Well, I don't know. I don't really have the faintest idea. Everybody who entered the program would have got the matching-to sample procedure throughout their stay, would have been assessed on your (Connors) rating scale throughout their stay, would have been assessed on the other behavior rating scale throughout the stay, would have had the classroom measures taken throughout their stay, and I at this point don't know how many people would have been partitioned out to meet... any of this.

Regarding the report of progress in the first year of grant support, Dr. Breuning acknowledged that it was misleading and probably inappropriate. He said that he had not understood the importance of it, that when he questioned the Pittsburgh grants office, he was told it was "no big deal.... write something up and send it in," and that is what he had done. He also said that because of personal problems he had not paid much attention to it and could not defend it. When it was pointed out to him that the instructions accompanying the form for that report were quite detailed and he was asked if he had seen the entire packet (for reporting progress and requesting the second year of recommended grant support), Dr. Breuning said that, to the best of his recollection, he had never seen the instructions. In answer to a question about whether the University of Pittsburgh provided any instructions or assistance for filling out such forms, he said, "None was offered, and I didn't know to ask for any." Interviewed on March 19, 1986, Ms. Carol Kaufman, Assistant Director for Research, WPIC, said that principal investigators there were provided with the entire application package and that Dr. Breuning was in the habit of checking with her in great detail on grant-related matters. The Panel noted that both of the progress reports were well-prepared and quite detailed.

Dr. Breuning told the Panel that the application received by NIMH on October 1, 1983, was submitted in error. He had been preoccupied by personal matters and "was just doing things to get them done." Dr. Breuning told the Panel that when he wrote the original version he "sat down with ... data and looked at it and projected what it potentially means or could be done with it." When asked about such specific statements as "During the 14 months of the project we have completed six studies and are about 65% through a seventh study," Dr. Breuning indicated that he felt the issue was one of semantics and that writing up preexisting data could be considered completion. He said that, to the best of his recollection, the statement in the seventh study indicated the number of people he projected to himself on whom he had "at least normative data." He acknowledged that the intent of the grant was not to write up data collected almost 10 years previously. He said that he had not attempted to willfully deceive or mislead anybody and that he had not been taught or instructed to take such a document seriously enough, and at the time he was "personally and academically not caring enough."

According to Dr. Breuning, about September 24 or 25, Dr. Nuffield expressed concern about the numbers of subjects reported. Dr. Breuning said that he revised the report on September 26 and that he left the revision with his secretary, Ms. Wilma DiPietro, when he went out of town, and she must have submitted the wrong version to Ms. Carol Kaufman. He said he had only the first, or face page, of the application when he signed it. He said he discovered the error only some 10 weeks later when he was attempting to withdraw the application and that he told the Department Chairman, Dr. Kupfer, about it. Dr. Breuning gave the Panel copies of two versions of the revision: One, with a handwritten date of September 26, 1983, had handwritten changes and annotations; and a second, with a handwritten date of September 28, 1983, had typed changes. The former is paginated, from pages 27-50. The latter is not paginated.

The application received by NIMH on October 1 has Dr. Breuning's signature and is dated September 27. It was signed by the Director of the University's Sponsored Projects Administration, Office of Research, September 29. The relevant pages are 27-50.

When asked to clarify the difference between the revised report he had given the Panel and the one actually submitted, Dr. Breuning said:

> The major difference is, the original one, in my opinion, now looking back, is grossly exaggerated from the standpoint that it takes a certain set of data and probably does more partitioning than you've seen of it than would be called for. For example,

> if you have four measures on one subject, taking that subject and using him in four papers for four different sets of analyses in one paper. And how it is presented in those different studies does not depict the fact that who is in number one is in number two is in number three.

When asked where and when the data were collected, Dr. Breuning said between late 1974 and early 1977 when he was finishing his doctorate in Chicago. He said that he had permission from various schools and administrators to collect various data and measures. He said:

> It was not a drug manipulation project I was coordinating. It was something that I sort of stumbled onto that I don't know who was doing it, somebody, I believe, completing an M.D., Ph.D., or some other degree at one of the area medical schools....

Dr. Breuning at first told the Panel he had data on some 25-30 subjects (the seven reported studies, if discrete, required 99; if not, at least 49), but later in the same interview he reduced the number to 15. He said some of the schools were public, some private, some institutionally affiliated. He could not, when asked, provide the name of any school or institution, nor could he name the investigator(s) who were conducting the studies. When asked whether data were collected from hospitalized children, he indicated that the use of the word "hospitalized" had changed. He had no raw data or identifying data for the subjects, and the summary data sheets he showed the Panel were not dated by year. When asked about the availability of experimental rooms of precisely the same characteristics and measurements in such a variety of sites, he said they were approximately the same. The studies reported FR and MTS procedures and described apparatus in detail. Dr. Breuning said that he carried portable experimental apparatus with him, and had used a different methodology, a "three stimulus flip card kind of apparatus, similar to what you would find in a (the) French pictorial intelligence test or something like that." Dr. Breuning said that, with the exception of the rating scale data, and with a few other exceptions, he had collected all the data himself.

Regarding consent, Dr. Breuning said that he had consent from the schools to do clinical, not experimental, assessments, but that he hadn't kept them, and that he had asked and been told that there was parental consent for drug studies. He maintained that he was involved with clinical assessments and said that he did not know that consent was required for psychological assessments.

In the context of this discussion, he said that he did not regard his work in Chicago as research, but as "quasi-experimental" or "quasi-normative" clinical data collection.

The studies in question reported counter-balanced drug and placebo; he was unable to say who wrote the drug orders. Nor could he say whether this was a single study or studies by different investigators. When asked if he could name any single individual who could verify the study, he said he could not. Later in the same interview, he gave the Panel the names of two individuals who could attest to his doing such work in the Chicago schools during that period, Dr. Paul Koutnik, an academic adviser, and Dr. John Regan, who had a nearby office when he and Dr. Breuning were doctoral students and with whom, Dr. Breuning said, he often discussed his work.

When asked by the Panel specifically about the first three studies reported in the progress section of the application received by NIMH on October 1, 1983, Dr. Breuning said that they were "virtually the same except for age differences" and that Study 3 reported on the same subjects as Study 2 but he had dropped one condition because he did not have all the measures on it. Dr. Breuning could not provide the Panel with either information or explanation of the subjects in Study 1 (which reports on children ages 6.8-14.3) and in Study 2 which reports on adolescents (whether they were in the same or separate classrooms, etc.). When asked if he could clarify who the subjects were in studies 2 and 3 (whether the same children were subjects), Dr. Breuning said he thought it possible but was not sure it was worth his time to do it.

Further discrepancies regarding the number of subjects reported emerged in discussion with Dr. Breuning. For example, Study 4 reports on 24 children ages 6-12; Study 3 on 13, ages 14-18; and Study 6 on 12 under the age of 6, making a total of at least 49 separate subjects required. Dr. Breuning's summary data book included data on only 30 subjects.

Dr. Breuning was asked about a reference, in the published report of Study 1, to a 1982 paper on recommended doses of methylphenidate in light of his claim that data were collected in 1974-1977. He responded that a reviewer had suggested putting in a reference regarding doses, that it was the reference "we happened to pick to use," and that he didn't "know if it is a big deal."

Regarding the revised progress report, both Dr. Breuning and Dr. Robert Sprague told the Panel that Dr. Sprague visited Pittsburgh in September 1983, and reviewed with Dr. Breuning the progress report. Dr. Sprague said that on September 23 he was given a copy of the same report received October 1 by NIMH, and on September 24 he discussed it with Dr. Breuning. He said Dr. Breuning displayed great pride in the report and continued to do so in subsequent conversations with him until December 3, when Dr. Sprague specifically questioned his work.

Dr. David Kupfer was asked if Dr. Breuning had told him about either patient flow problems or the revised progress report. He stated that prior to December 1983, Dr. Breuning had not discussed a patient flow problem with him, had not told him the studies described had not been carried out, and did not tell him about either a need to revise or a mistaken submission of a progress report. He said he had no indication of a problem until Dr. Sprague telephoned him in early December 1983. He also said that it was clear to all investigators there that they were to follow the protocol in their applications, that any problems in doing so were to be brought to his attention, and that progress reports were to reflect precisely the status of the research being conducted. He denied that anyone at the university held a casual view of progress reports.

At a March 19, 1985, meeting, Ms. Kaufman reviewed carefully the two versions of the revision, one provided by Dr. Breuning and one from her files. There was no file record of a revision.

Ms. Wilma DiPietro, Dr. Breuning's former secretary, was also interviewed on March 19. She, too, was shown copies of the progress report in its original and revised forms. She said that she had no recollection of any changes being made in the progress report and that this was the first she had heard of the claim that it was her error which had caused so many problems for Dr. Breuning. Upon careful examination of the documents in question, Ms. DiPietro determined that she had not typed them. She pointed out that she always used the lower case "1" for the numeral one, where the numeral one was used throughout in the revision. Ms. DiPietro recalled that Dr. Breuning frequently did his own typing and that he had maintained his own files.

The Panel contacted the two individuals who Dr. Breuning had said could vouch for his work in Chicago. Dr. Paul Koutnik said he had been Associate Professor of Education at Illinois Institute of Technology from 1976-1979, was an outside adviser on Dr. Breuning's thesis committee, and, as part of his regular duties, had placed Dr. Breuning for student teaching in biology in the Bloom Township, Illinois, high school, probably during 1976-1979. Dr. Koutnik knew Dr. Breuning did contractual work in the school system, measuring the positive reinforcement effect of rewards on school performance of special education students. He knew of no other research involving human subjects by Dr. Breuning and had no involvement in making arrangements for such research. Dr. John Regan knew Dr. Breuning both in graduate school and at the Oakdale Regional Center. Dr. Regan knew of no such work in the Chicago schools.

At Dr. Koutnik's suggestion, the Panel contacted Dr. Allen Wolach, Chairman, Department of Psychology, Illinois Institute of Technology, who had been chairman of Dr. Breuning's Ph.D. dissertation committee. Dr. Wolach said he had no knowledge of any drug studies in which Dr. Breuning might have been involved in the Chicago schools or elsewhere.

Panel findings: Dr. Breuning acknowledged to the panel that none of the studies he reported from the University of Pittsburgh had been carried out there. His claim that he had gathered the data in Chicago area schools, which he could not name, between 1974-1979, as part of an effort incidental to studies by investigator(s), whom he could not identify, is not credible. The Panel checked widely and carefully and found no corroboration at all of his account. The Panel, therefore, concludes the data were not collected.

Dr. Breuning admitted that he could not defend a progress report on work under his first year of grant support that specifically describes work he had not done. His explanation that he was inexperienced and uninstructed does not agree with the Panel's observation of administrative practice at Pittsburgh or with the detail and polish of the report.

Dr. Breuning prepared a highly detailed and very specific report of progress for his renewal application of work that had, in fact, not been done at Pittsburgh at all and that, at best, misreports and misrepresents other work. The Panel found no evidence that the revised progress report given it by Dr. Breuning existed before his work was called into question by Dr. Sprague and the latter had communicated his concern to NIMH.

Dr. Breuning's account of why he had not carried out the studies at Pittsburgh, as proposed, does not agree with his application for funds for 4 more years to continue the same kind of studies, on the same kind of patients, and in the same unit.

For the above reasons, the Panel concludes that Dr. Breuning's preparation of two grossly distorted progress reports could only have been a deliberate and intentional effort to mislead and deceive NIMH.

APPENDIX K
SUBCONTRACTS TO UNIVERSITY OF PITTSBURGH

SUBCONTRACTS TO UNIVERSITY OF PITTSBURGH

As noted on page 8 of the Report, subcontracts, under MH-32206, with the University of Pittsburgh for collaborative research were active in the 03, 04, and 05 years of the grant. Between July 1, 1981, and November 30, 1983, a total of $51,333.03 was paid to the University of Pittsburgh. Of this amount, $2,147.50 was for partial payment on computer equipment. The balance was for salary support of three staff members, Sue Ann Fultz, Lori Sisson, and Vicky Davis.

The stated objectives for this subcontracted work were: 1) examine the incidence and severity of dyskinesia following psychotropic drug withdrawal, 2) examine the effects of psychotropic drugs on laboratory measures of learning and performance (i.e., matching-to-sample tasks), 3) examine the efficacy of psychotropic drugs alone and in combination with nondrug therapies for treating aggressive/psychotic and other inappropriate behaviors, and 4) gather data to be used in establishing the reliability and validity of the RBRS (Resident Behavior Rating Scale).

The Panel confirmed through interviews with the three individuals paid under the subcontract, that DIS-Co assessments and matching-to-sample tests were carried out on all patients in the Merck Unit at the University of Pittsburgh. However, Dr. Sprague told the Panel that he received no useful data from the subcontract and Ms. Davis told the Panel that no data were sent to Dr. Sprague. Dr. Breuning told the Panel that stimulant followup studies were not carried out for the same reasons he had not carried them out under his own grant (see Appendix J) and that the University of Pittsburgh, through the Department of Psychiatry, stopped the contract work because no funds were ever provided by Dr. Sprague. (He said that he and the staff continued collecting data on their own.) This contention was not supported by records at the two universities which show invoices submitted and paid in the amounts indicated above.

Panel comments and findings. The Panel believes that there are issues of grant and contract oversight and accountability involved rather than of scientific misconduct. The University of Illinois appears to have regularly paid on a series of subcontracts although no useful product was received. The Panel recommends that NIMH take appropriate administrative action to follow up on this matter.

APPENDIX L
COMMENTS

March 24, 1986

Lorraine B. Torres, Director
Division of Extramural Activities
NIMH
Room 9 - 105, Parklawn Building
5600 Fishers Lane
Rockville, Maryland 20857

Dear Ms. Torres:

Attached please find my response to the preliminary report prepared by the NIMH investigatory panel. I believe it is self explanatory and I hope that all the recent press has not reduced the liklihood of complete objectivity and fairness by NIMH.

Sincerely,

S. E. Breuning

Stephen E. Breuning, Ph.D.

Attachments

Response to NIMH Investigatory Panel Preliminary Report

In the following pages I have responded at length to the preliminary report by the NIMH investigatory panel charged with the investigation of an allegation of misconduct. Such a task is one that no one should have to engage in and each member of the panel I am sure found it uncomfortable.

The report is lengthy and weighty, and the investigation was very costly. The report states itself as comprehensive. While I do not envy the panel members and I appreciate their best efforts, it is clear that they are not trained detectives and I have concerns with the investigation that I must mention prior to dealing with more specific issues.

One concern is the panel did not seem to be able to assess issues independent of their narrow and personal views of the specific issues. Some of these are dealt with immediately below and throughout my response. I am constantly being judged by standards which do not exist.

Second, the style of interview utilized by the investigatory panel was one of threat and intimidation. I do not know if this intentional or not. I have spoken with most coauthors since they were interviewed. Each told me that they felt highly threatened, ganged up on, and almost forced to respond in a certain manner. Dr. Poling told me that he felt that they had decided I was guilty and would have to prove innocence. Dr. Gualtieri had warned me very early on that in these circles one is always guilty until proven otherwise. Dr. Cullari told me that he felt it is clearly a witch hunt and that the panel members need to review the real world. Ms. Davis said that two and three questions always came at once and she rarely had time to answer. She also said that every time she gave a positive response she was asked about a conspiracy. This is also what Dr. Cullari stated. I know from my own interview that I felt each of these issues and raised them during my interview.

I know this sounds like sour grapes and I had dismissed most of this until I received the preliminary report. After reading the report and reviewing all of the accompanying interviews and information, I was shocked to see that all positive comments do not appear in the report and that unrelated events and statements had been placed together to form a totally one-sided negative view of the situation.

Not once was I asked to supply a list of character witnesses or was any attempt made to assess me as a person, teacher, administrator, and researcher. No one ever attempted to determine if others believe me capable of what this preliminary report suggests. I am more than willing to supply any number of statements as to my abilities, integrity, religion, and ethics. How dare this investigatory panel have the audacity to attempt to only judge part of a person.

Third, the investigatory panel continually asked the wrong questions, sometimes to wrong people sometimes to correct people. Often the right question was asked to the wrong person. No wonder there is confusion and alot of people who could not answer on my behalf. Also, this is why there was often confusion over where people recollected things were done. This confusion often was the direct result of improper/incomplete question and no opportunity for me to be present to help jog other people's memory.

Related, it is clear from reviewing the statements made by many interviewed at Coldwater and Oakdale that not only where they unable to confirm things they should know little about, they were unable to confirm things they should. For example, Dr. Niblett at Coldwater said he had never heard of the DIS-Co, it it was developed and widely used at Coldwater — including the building in which he worked.

Further, my direct supervisor at Coldwater (also a coauthor) was never interviewed. The person who largely supervised me at Oakdale was only given a very brief telephone interview. As can be seen in the sections which follow they fully support what I have done. Also, my immediate supervisor at WPIC was never interviewed.

Fourth, much, if not most, of the investigatory panel's focus was on the use of placebos and double blind conditions. From the way they discussed this issue with me and the others they interviewed, it is clear that their definition and portrayal of these issues is dramatically more limited than my own. There was never the opportunity to discuss this or any topic in detail.

First the placebo. It has always been my understanding that a placebo is an object or substance which contains little or no medication (drug) and is used to determine a psychologically controlled response by the client. If I were to only think of a placebo in terms of what I could have done at a sophisticated place like WPIC, I would think of detailed involvement from a pharmacy where elaborate procedures would be in place to allow for the complete realm of possibilities. Is this constricted view necessary or correct. No.

For example, take an individual who receives medication which is crushed or placed whole in some pudding, applesauce, or juice and administered. After a period of time the dosage is reduced and ultimately discontinued. Throughout this reduction whatever the dosage is, it continues to be administered in the pudding and the pudding continues to be administered after the actual use of the drug has stopped. Is this not the use of a placebo condition? To me it most certainly is. Similar applications using juices and crushed or liquid medication allow for all types of blinding procedures and advance preparations (e.g., month at a time) which would require no pharmacy documentation. I know of no standard which would contradict this. The only confusion is that this is not what investigatory panel members had on there minds. These types of placebos is what I had typically used or found to often be used routinely. There were though occasions where pills were actually placed in empty capsules and then the capsules used alone. Never without physician awareness. Here again I know of no standard which would establish that this was inappropriate. And finally, in some cases placebos were set up at the given pharmacy. I know of no Oakdale of Coldwater polices which necessitated specific documentation on this.

A double blind condition is a condition where text books say the patient and physician are unaware as to whether or not an active drug or placebo is being used. In more common usage a double blind condition would also be where neither the patient nor observer/data collector are aware as to whether or not a drug or placebo is being used.

If one adopts these parameters and couples them with the information presented throughout the various sections of this response, there should be little or no confusion of this issue.

Fifth, the investigatory panel continually states that they found no evidence of consent. Yet, as stated later in this response, in no case did they identify one specific instance where consent was not obtained. Thus, the logic that because they didn't find it I did something wrong is not tolerable. Consent can take verbal or written forms. No one any where I have ever worked, patients, parents, or staff, have ever stated that I provided anything less than the utmost respect and concern for this right. Wherever I stated consent was obtained it most assuredly was.

And sixth, the investigatory panel continually used nonexisting standards to judge me against. Every investigator, every clinician, and every administrator has an obligation to do the utmost to protect client confidentiality. This is what I have done in all cases. Throughout their report the investigatory panel has taken issue with the fact that raw data are not available. I contend, and will repeat throughout, that this is ridiculous. When I interviewed with the investigatory panel I asked (as did others) to what standard are they referring. What are the timelines? One year, two years, ten years, etc. The panel was unable then and now to answer this question. There is no answer. If one takes the panel's position to the logical extreme one would have to keep raw data and client identifications available forever. Thus, any investigator who discovered that raw data from a study, lets say published five years prior, had been lost or destroyed they would be under an obligation to retract the study. This is obviously absurd! There are many other similar issues discussed throughout my response.

The members of the investigatory panel are grossly mistaken if they believe that it is common practice for individuals to keep their records and data for very long after a paper is published.

Pharmacological Studies

I. I think that is important to begin this section by listing the published studies which prior to this response the investigatory panel has neither found nor supported evidence of problems.

A. Ferguson, D.G., Cullari, S., Davidson, N.A., & Breuning, S.E. Effects of Data Based Interdisciplinary Medication Reviews on Prevalance and Pattern of Neuroleptic Drug Use with Institutioinalized Mentally Retarded Persons. Education and Training of the Mentally Retarded, April 1982, 103-108.

B. Wysocki, T., Fuqua, W., Davis, V.J., & Breuning, S.E. Effects of Thioridazine (Mellaril) on Titrating Delayed Matching-to-Sample Performance of Mentally Retarded Adults. American Journal of Mental Deficiency, 1981, 85, 539-547.

C. Davis, V.J., Poling, A.D., Wysocki, T., & Breuning, S.E. Effects of Phenytoin Withdrawal on Matching-to-Sample and Workshop Performance of Mentally Retarded Persons. Journal of Nervous and Mental Disease, 1981, 169, 718-725. And, Davis, V.J., Psychopharmacology Bulletin, 1982, 18,51-54.

D. Sprague, R.L., Kalachnik, J.E., Breuning, S.E., Davis, V.J., Ullman, R.K., Cullari, S., Davidson, N.A., Ferguson, D.G., & Hoffner, B.A. The Dyskinesia Identification System - Coldwater (Dis-Co): A Tardive Dyskinesia Rating Scale for the Developmentally Disabled. Psychopharmacology Bulletin, 1984, 20, 328-338.

On this study I wish to add a comment. The investigatory panel states in their report that "The inclusion of Dr. Breuning's name appears to be an acknowledgment of his role in the pilot studies at Coldwater". It is important to note that the DIS-Co was completely developed at Coldwater and on all early drafts of the manuscript for this publication I was listed by Dr. Sprague as the first author. It was only at my recommendation that the above listed order of authorship be used. In his interview with the investigatory panel Dr. Sprague states that I (and Coldwater staff) developed the DIS-Co.

I never made any attempt to minimize my involvement in this grant and project. If it were not for my involvement and the involvement of the Coldwater staff, the DIS-Co, the RBRS, and all training tapes would not have been developed. These are what the subcontract called for.

Second, I will now review and comment on the following studies. These studies will be discussed together because the investigatory panel is confused over the same issues in each. Prior to discussing the following studies I wish to reiterate that no NIMH funds have been spent on them. The grant MH-32206 is only referenced at Dr. Sprague's request.

It was my understanding that this was proper because we were working together on this grant, because the issues were related, and because he was paid by the grant and he reviewed each paper prior to its publication. If this was wrong I apologize. But I honestly gave it little thought since the same practice was commonplace at WPIC and most other places I know of.

A. Breuning, S.E., Ferguson, D.G., & Cullari, S. Analysis of Single-Double Blind Procedures, Maintenance of Placebo Effects, and Drig Induced Duykinesias with Mentally Retarded Persons. Applied Research in Mental Retardation, 1980, 1, 175-192. Brief report version in Psychopharmacology Bulletin, 1981, 17, 122-123.

B. Breuning, S.E., Ferguson, D.G., & Cullari, S. Analysis of Single-Double Blind Procedures, Maintenance of Placebo Effects, and Drug Induced Dyskinesias with Mentally Retarded Persons - A Brief Report. Psychopharmacology Bulletin, 1981, 17, 122-123.

C. Breuning, S.E., O'Neill, M.J., & Ferguson, D.G. Comparison of Psychotropic Drug, Response Cost, and Psychotropic Drug plus Response Cost Procedures for Controlling Institutionalized Mentally Retarded Persons. Applied Research in Mental Retardation, 1980, 1, 253-268.

D. Breuning, S.E. & Davidson, N.A. Effects of Psychotropic Drugs on Intelligence Test Performance of Institutionalized Mentally Retarded Adults. American Journal of Mental Deficiency, 1981, 85, 575-579. (Some confusion exists over where I stated this study was performed. These data were from Oakdale and Coldwater).

The investigatory panel seems to be discounting these studies for several reasons. These will be discussed individually below.

1. No plausible site for the execution of the studies was identified.

The investigatory panel was unable to find the sites of the studies plausible because (a) they asked the wrong people questions, (b) when they did speak to the proper people they typically asked wrong or improperly stated questions, and (c) they failed to utilize supportive evidence they themselves found.

At neither Coldwater nor Oakdale was my primary supervisor interviewed or interviewed in any detail. I recently spoke with Dr. M. O'Neil who was my direct supervisor at Coldwater. He says that he was never contacted by NIMH. This is odd because in addition to being my direct supervisor he was also a coauthor on one of the papers reviewed by the investigatory panel.

Dr. O'Neill says that he can absolutely support the following:

a. That there were ongoing sophisticated behavioral programs.

b. That there was ongoing systematic data collection. (The investigatory panel itself reports in it notes that "A random review of patient charts indicated that behavioral observations were carefully and frequently recorded").

c. Routine use of the DIS-Co as well as the regular use of another dyskinesia/side-effects scale. (He thought it was called something like the ESC or ISC but was not sure. This is obviously the same as the reported use of the WESC).

d. That placebos were regularly used in Building 42 and elsewhere at Coldwater.

e. That Coldwater had no policy whatsoever on the use of placebos.

f. That intelligence testing under both standard and incentive conditions was standard practice with some of the psychologists.

Dr. D. Nolley was for the most part my direct supervisor at Oakdale. He was briefly interviewed over the telephone by one member of the investigatory panel. Dr. Nolley told me that he was asked what research activities I was involved in at Oakdale. He said he described primarily the fish research because the way the question was phrased he thought that it pertained to things which would have had to have gone through the research committee. It did not occur to him that he was being asked about the reporting of data collected as part of a client's clinical assessment and treatment program. With this in mind, Dr. Nolley told told me that he recalls the following:

a. That there were ongoing sophisticated behavioral programs.

b. That there was ongoing systematic data collection. (It is worthwhile for me to point out here that the data collection procedures used widely at Coldwater were identical or nearly identical to those used ay Oakdale. These systems were primarily developed by Dr. Nolley).

c. That I was interested in drug side-effects when I came to Oakdale and that I used some instrument. He does not recall what the instrument was called or actually how often it was used.

Mr. Rogan, Director of Coldwater, has told the investigatory panel that I had knowledge of and interest in tardive dyskinesia prior to coming to Coldwater.

d. That placebos were sometimes used at Oakdale. He recalls physicians often talking about there use. Further, he said that placebos were frequently used if one includes situations where the medication had been being given in pudding or applesauce and the use of pudding or applesauce continued after drug discontinuation.

e. That intelligence testing under both standard and incentive conditions was of interest to many of the psychologists and routinely done.

Further, Dr. Nolley will verify that the information gathered by the investigatory panel at Oakdale with respect to my work location is incomplete. He clearly recalls my initially working in 34E, but also periodically 34W, and later on regularly in several other Buildings. He thought Buildings 5, 6, 8, 10, and 11 but is not completely sure if these Building numbers are completely accurate. Best I can recall, at least 5, 6, and 8 were male buildings.

One additional point here, I recently spoke to Dr. J. Regan at Oakdale. He was interviewed by one member of the investigatory panel. He, like Dr. Nolley and most people interviewed at Oakdale, interpreted the questions to pertain to issues other than clinical practice. I asked Dr. Regan what he would say if questioned about such issues from a clinical standpoint and he commented "Why would anyone expect me to know anything about it". This is a key point since a majority of the people interviewed at these two sites could logically answer "No" or "I don't know" to a series of questions they should have no answer to.

2. Coauthors did not see raw data.

Exactly why this is an issue I am not quite sure. According to the investigatory panel's information from interviews all coauthors on these studies stated that they have never asked to see the raw data. If any of them would have asked they certainly would have been shown it.

The investigatory panel seems to be implying that there is some standard which obligates one author to say to a coauthor "Hey, do you want to see the raw data". If this standard exists it is new to me. It is also apparently new to others such as Dr. Sprague who never offered to show me the raw data from Cambridge. What does this mean? Nothing! I am confident that Dr. Sprague would have shown me the raw data had I asked. Just as I would have with the coauthors of these studies. Similarly, I have coauthored several papers with Dr. Poling and Dr. Matson. I never saw raw data, consent forms, etc. They never offerred, I never asked.

Not one coauthor has raised a question about about any aspect of these studies prior to publication, since publication, or since being interviewed and questioned by the investigatory panel. Further, each of these studies was reviewed by Dr. Sprague in prepublication form and no concerns of any kind were raised.

3. No evidence of Research Committee approval.

There is no component to any of these studies which would have required research committee review and approval at either Oakdale or Coldwater. Since there were no manipulations of any kind outside of the client's clinical plan and no policies in place which required research review for placebo use, it would be the oddity for the research committee records to have any mention of these studies.

With respect to consent, the investigatory panel continually states that they found no evidence of consent. Yet, they have provided no evidence of a single client who participated without consent. It is not reasonable for the panel to continually make such an unsupported statement.

Additionally, it was not even the policy at The University of Pittsburgh School of Medicine for placebo use to be considered research per se. The Medical School Human Rights Committee told me (in a letter from Dr. J. Lewis Chairperson) that placebo use did not require consent at Pitt if its use was clinical.

4. Facility policies prohibiting the use of placebos.

Neither Coldwater nor Oakdale had policies on the use of placebos. This is clearly evident from the interviews conducted. Further, in a letter dated 2-13-87 from Dr. Davidson at Coldwater to me he states that there was/is not a written policy on the use of placebos — only a "... general practice...".

5. Method section does not identify where the subjects were from.

Again, I find it hard to understand the issue here or the standard to be adhered to. For sake of comparison I reviewed articles in several journals to see how my methods sections differed from others with respect to this issue. I found the following:

a. ARMR, 1980, 1. Two of my articles are published here. Of seven other studies three were more specific than me, four were not. In a randomly selected issue of this journal (1985,6,1) five of studies utilizing a research design were no more or less specific than I was.

b. AJMD, 1981, 5. One of my articles is published here. Of seven seven studies reviewed three were more specific, three equal, and one I was not sure how to classify. More recently, again just grabbed off the shelf (1985,89,5), four were more specific and seven were less specific.

c. AM. J. Psychiatry, 1982, 139. One of my articles is published here. I randomly selected seven of the research articles, all seven were the same or less specific than I was.

Is there an issue here? Obviously not. Interesting enough, many of the articles I found to be of equal or less specific contained an NIMH or other granting agency reference.

In concluding this section I wish to add that at no time has the investigatory panel had any concerns with the outcomes of these studies. That is, no one has questioned the results per se. Further, there is not a finding reported in these studies which has not been replicated by myself and many others.

Thus, there is no logical way in which this investigatory panel can substantiate or conclude that there are problems with any of these four studies.

II. There are other three studies which the investigatory panel raised each of the above issues. These three studies will be addressed separately because some additional comments are required. As with the studies listed above, no NIMH funds have been spent on any aspect of these three studies. The grant is referenced for the reasons already stated.

A. Breuning, S.E. An Applied Dose Response Curve of Thioridazine with the Mentally Retarded: Aggressive, Self-stimulatory, Intellectual, and Workshop Behaviors - A Preliminary Report. Psychopharmacology Bulletin, 1982, 18, 57-59.

The data utilized in this paper are extrapolated from several sets of data reported elsewhere, but primarily associated with the data sets collected as parts of the two studies listed below. Specific issues relevant to one are relevant to all and are discussed below.

B. Breuning, S.E., Davis, V.J., Matson, J.L., & Ferguson, D. G. Effects of Thioridazine and Withdrawal Dyskinesias on Workshop Performance of Mentally Retarded Young Adults. American Journal of Psychiatry, 1982, 139, 1447-1454.

Best I can recall, Part I of this study was conducted at Coldwater while Part II was conducted years earlier in Illinois. With respect to Part I, I do not believe there are any grounds for concern. It has been established that the site is plausible. In addition to what has been discussed above on this issue, the investigatory panel has clearly established the availability of the workshop and my access to its records. Second, the coauthors seeing raw data continues to be irrelevant. Third, research committee approval not applicable. Fourth, placebos were clearly used. Fifth, specificity of the method section is not at issue. Sixth, the issue of neurological/PT evaluations is clearly supported by the statements of Mr. Rogan and Dr. Davidson. However, seventh, the statement that the diagnoses were DSM III is an error. I am not sure how I made this mistake but it did indeed occur. It most assuredly was not intentional and I will take appropriate actions to correct the situation. With respect to Part II, the same error is present with respect to diagnoses and again I will take appropriate actions to correct the situation. However, these errors have no impact on the overall outcomes.

Part II of this study reflects data I did indeed collect in Illinois towards the end of my schooling there. I cannot after this lengthy period of time state the site(s) of the data collection with certainty. I have not had the time, money, or quite honestly the interest to attempt to retrace these steps. There is no reason I should be expected to. It is verifiable that during the time period in question I taught at Trinity College and had students do at least brief practicums at numerous mental retardation sites in and around Chicago. This is what led to initial access to sites where much data could be accessed directly and retroactively. The only other supporting documentation I can off here is a copy of a notes page from the back section of a May 14-17, 1977 Midwestern Association of Behavior Analysis Convention held in Chicago. This page appears in Appendix 1 and reflects my initial interview with Dr. Nolley. The notes state that we discussed some workshop/drug data, drug/IQ data, and stimulant data that I had been collecting. I inquired as to the feasibility of continuing such at Oakdale. He and the Director of Oakdale, Mr. Ethridge, told me such continuation, if clinical in focus, would be supported. Dr. Nolley tells me that he recalls this conversation fairly well.

C. Breuning, S.E., Ferguson, D.G., Davidson, N.A., & Poling, A. Intellectual Performance of Mentally Retarded Drug Responders and Nonresponders. Archives of General Psychiatry, 1983, 40, 309-313.

As with the study above, the statement that the diagnoses were DSM III is in error. I will take appropriate actions to correct the situation. Although again, this error does not impact on the conclusions. Also, this study includes data collected in Illinois. The relevant issues are stated above.

Up until now, and with respect to only this last study, no coauthor has raised any concerns. In reading the investigatory panel's report I find that Dr. Poling had sent a letter to the journal stating that he had misgivings about the scientific merit of this study. I was surprised to see this because it is a direct contradiction to what he told me in a telephone conversation one week after his NIMH interview. In this conversation he told me the interview was very intimidating and the investigatory panel had told him he should write a letter to the journal stating that he had concerns. He told me he really did not have any concerns but he did not know what to do because he needs grant money to do his work. Dr. Poling has never mentioned concerns to me and I believe that his letter would have never been prepared if it were not for the at least tacit pressure of the investigatory panel.

In concluding this section I wish to repeat that the investigatory panel is holding me to standards which do not exist. I know of no standards which state how long an investigator is to keep raw data and records after a study is published. The vast majority of people I know state that they rarely keep such information for more than a year or two after publication. In asking people about this over the past years the typical responses included things like "six months without a reprint request" to "after six months the information is put into a box and in another six months the box is discarded". Without debate it is the investigator's responsibility to ensure confidentiality, and if no questions or concerns have been raised within a reasonable time frame (a year or two following publication is more than sufficient) there is no compelling reason to not destroy the records.

III. I would next like to review the following study:

> Davis, V.J., Cullari, S., & Breuning, S.E. Drug Use In Community Foster-Group Homes. In S.E. Breuning & A.D. Poling (Eds), Drugs and Mental Retardation, Springfield, Ill., Charles C. Thomas, 1982, 359-376.

As with the studies discussed above, no NIMH funds have been spent on this study. Grant MH-32206 is referenced for the reasons already given.

The investigatory panel seems to be discounting this study for the following reasons which are individually discussed.

1. Coauthors did not see raw data.

The same issues discussed above on this topic pertain here. Both coauthors state that they never asked to see the raw data. They also have not had questions concerning the data prior to or subsequent to the investigation. In its report the investigatory panel quotes Dr. Cullari as saying "he thought that Dr. Breuning had conducted part of the study but maybe he made up the rest". Dr. Cullari told me that he did not make this statement. What he said was "maybe he made up the rest, butt I don't think so". I attempted to clarify this by reviewing the transcript of Dr. Cullari's interview with the investigatory panel which the panel supplied me. At least in the transcript sent to me there was no such quote found as the one they attributed to Dr. Cullari.

2. Dr. Breuning unable to provide the name of at least one person who participated in the study.

During my interview with the investigatory panel I was asked to "name one person who participated in the study". At the time the only name I could recall after 6/7 years was F. Morris. I had asked the investigatory panel prior to my interview to supply me with a list of questions so that I could do some homework and be prepared. At no time was the investigatory panel willing to do so. Thus, answering detailed and specific questions from so long ago would obviously be difficult. I only recalled Mr. Morris' name because it occurs in the chapter. I never told the investigatory that Mr. Morris had been involved in the research.

In the interview Mr. Morris was told that the chapter names him as one of the people who provided training for managers of the group homes. Mr. Morris denied this and said he had only had me speak at a seminar.

Two comments. First, the investigatory panel totally misrepresented what the chapter says about Mr. Morris. No wonder he denied the role. It was not the role he had. Second, the chapter clearly states that Mr. Morris worked with me to hold a training seminar through his community mental health agency. Thus, Mr. Morris' comments to the investigatory panel clearly confirm his role exactly as described in the study.

In the brief time I have been allowed to prepare this response, I have had time to contact two people who can substantiate this study. I first contacted P. Miller from the Association of Retarded Citizens. She tells me that she vividly recalls reviewing the community data with me. She recalls our comparing drug use with discharged Coldwater clients before and after their discharge. Also comparing them with other clients in the community. She said she recalls how alarmed she was at the high drug use in the community and how little supervision and monitoring there was (what we are talking about is her direct observation not a reading of the chapter). Further, she said she remembers how our reviewing records together and discussing issues impacted on her awareness of the problems and resulted in her agency drastically altering how they deal with these problems.

I had a similar discussion with Dr. B. Uhlman, Director of Residential Oppertunities, Inc. Dr. Uhlman clearly recalled providing me demographic information on the clients in his program. He stated that when we reviewed the drug programs his clients were on it was the first time he really understood the magnitude of the problem. As with Ms. Miller, he states that this data directly impacted on changes in their monitoring of drug use and staff training.

3. Expense of the study.

The investigatory panel has not told me how much they think this study should cost, but it seems as if they think it expensive. Maybe it would be expensive for them. While I can not recall with certainty, I estimate that the study would have likely cost about $700-800. The majority of this I just paid myself as I pursued this over the course of the year or so. Both coauthors stated in their interviews with the investigatory panel that they also did not understand the issue of expense. I believe that this is only an issue in the minds of people unaccustomed to directly doing the work themselves (this is not intended as a derogratory comment — only that things are much less costly when done without budgets to justify and no research assistants or students to pay).

4. Computer Center had no record of Dr. Breuning using the equipment.

On three occasions I telephoned the WMU Computer Center and told them I wished to verify my use of the computer facilities while I had an Adjunct appointment at WMU during 1979/1980. All three times I was told that it would be incredibly unlikely that they could provide this type of information. Further, both coauthors recall on at least one occasion being with me in Sangren Hall entering the data into the system.

In concluding this section it is clear that as discussed above the investigatory panel is confused only because of its own misunderstanding. Again, the investigatory panel has no questions as to the accuracy of the results. The only finding of this study not replicated by myself or others is the overall frequency of drug use in the community. This merely reflects the decline of drug use over the past six years. All other results have been replicated and can still be found in the majority of community programs today.

As before, there is no logical way that the investigatory panel can substantiate or conclude that there are any problems with this study.

IV. In this last section under Pharmacological Studies. Three issues need to be addressed. These include the ACNP abstract, and related article, the Behavioral Analogue paper which was never published, and the matching-to-sample paper which was not published. I will begin with the published article and related abstract.

> Gualtieri, C.T., Breuning, S.E., Schroeder, S.R., and Quade, D. Tardive Dyskinesia in Mentally Retarded Children, Adolescents, and Young Adults: North Carolina and Michigan Studies. Psycharmacology Bulletin, 1982, 18, 62-65.

Like studies already reviewed, this publication and abstract did not involve any NIMH funds. Unlike the others, an NIMH grant is not even referenced.

As with most of the studies already discussed, the investigatory Panel has the same confusions with this study as already reviewed. While it is necessary for me to be redundant in addressing these issues I will be as brief as possible.

1. Plausible site for the study.

In detail this has been addressed. All necessary data collection procedures, assessments, and required review processes have been discussed and it is clear that the data was very feasible collected at Coldwater and Oakdale. Some clients from both centers were included in this manuscript. The dyskinesia assessments were in place by me at both sites.

Dr. Gualtieri states that I told him that all clients were from Coldwater. I have never done so. I did not see any prepublication version of this manuscript and the first I knew of the statement about Coldwater was when I received a copy of the published article. I never mentioned this to Dr. Gualtieri because it just did not seem very important.

Until the data were presented at the conference I had not seen any of Dr. Gualtieri's data (analyzed or not) nor had I seen my own data analyzed. To the best of my recollection Dr. Gualtieri had performed all the analyses of my data from information I had sent him.

A copy of Dr. Gualtieri's initial analyses of these data, in his own hand, are attached in Appendix 2.

Additional analyses of the data by Dr. Gualtieri are attached in Appendix 3.

The investigatory panel reports that Dr. Gualtieri wrote to the editor of Psychopharmacology Bulletin, informing him that "Dr. Breuning had advised him of certain irregularities in the Michigan data". As I have repeatedly told Dr. Gualtieri, I have never advised him of any irregularities in these data. What he considers to be the irregularity is the absence of raw data after several years. Since there are no standards pertaining to this I do not consider it an irregularity.

All of the summary data and demographic information for this study are completely intact .

Dr. Gualtieri did indeed offer to go to Coldwater and review records. People seem to have trouble understanding that I certainly had/have no objections to him doing so; its just that without the client identifications I did not have a clue as to how he would review records. Prior to this situation Dr. Gualtieri had never asked for this information.

Given all of the above discussion coupled with the fact that Dr. Gualtieri's data and my data so closely replicate each other, and the majority of the published dyskinesia data also show the same effects, there is no logical or substantiated basis for believing that there are problems with these data.

Dr. Sprague's concern with the ACNP abstract was not with any of the prior published data but only with one sentence in the abstract which reads "Assessments were conducted on 45 of the clients at six month intervals fro an additional two years". No follow-up data per se ever appear in the abstract. As I have said repeatedly, the intent of the sentence was merely to say that there was some follow-up, it was very unsystematic, and that these casual observations seemed to show no changes. It is only Dr. Sprague's interpretation of this sentence which led him to become concerned. I had no intent for anyone to interpret this sentence in the way Dr. Sprague had.

After my conversation with Dr. Sprague I prepared a corrected abstract based upon follow-up data that was intact. I offered to present this abstract and publically correct the concerns and aany potentially misleading statements. Dr. Sprague convinced me that this would not be an appropriate thing to do. Obviously this is what I should have done.

There is a legitimate problem in the abstract with the statement about placebo/double blind procedures. It should have read that some of the clients had received placebo/double blind procedures. Also, the word "consecutive" should not have appeared in the sentence with "80 weeks". This is an error I made and did not catch. This abstract was prepared with little notice (I think Dr. Sprague notified me of his need for the abstract only two days prior to his needing it), rigid space and format requirements were specified, and the time period for preparing the abstract was at the tail-end of the 6-8 month period in which personal issues were just starting to get resolved (discussed elsewhere in this report). However, the fact remains that I was much less diligent in preparing this abstract than I should have been. I certainly was not intending to deceive anyone.

With respect to Dr. Sprague's concerns with this abstract, the investigatory panel must be reminded that as soon (within the week) as Dr. Sprague brought his concerns to me, I immediately informed Dr. Kupfer at Pittsburgh and I telephoned Ms. Natalie Reatig the grant project officer at NIMH to inform her. Before we discussed any detail she said that if it was not grant funded it was of no concern to NIMH. My only point is that I immediately notified all of the appropriate officials that a colleague had concern over part of this abstract and had begun to take appropriate remedial action.

The investigatory panel believes that there is an inconsistency in my telling Dr. Sprague that the data could not be located and my telling them that the data had been discarded. I will again clarify. What I told Dr. Sprague was "I have yet to locate the other raw data or the subject identification code sheet. This information is now three years old and has not been reviewed in some time". My response was phrased this way because all I could think about was thoroughly looking through all of the data and information I had for all projects in case I had kept the information. It must be remembered that Dr. Sprague had asked for a response within 2-3 days and I tried to show a good faith effort by sending him what I could within this time period. I never spoke to Dr. Sprague again on this issue but did tell Dr. Gualtieri and the review panel at Pittsburgh that I honestly do not know if I had discarded this information or if it had been lost in the move from Michigan to Pittsburgh.

A mistake was made in this abstract, without haste I attempted take appropriate action, the abstract was not presented. I do not know what else I could have done.

Gualtieri, C.T. & Breuning, S.E. A Behavioral Analogue of Withdrawal Dyskinesia. Psychopharmacology, in press. (Withdrawn in December, 1983)

When Dr. Sprague's confusion over the abstract began Dr. Gualtieri and I agreed to have him put the article on hold. Later on I told Dr. Gualtieri that if he wishes to withdraw the manuscript I did not care. However, there were no irregularities other than the one listed below. All of the summary data and demographic information remain intact. I told Dr. Gualtieri that there was one problem with the paper. This was that it states that all clients had received placebo/double blind withdrawals. Most had but not all. I had previously notified him of this in a June 14, 1983 letter (this letter has already been made available to the review board at Pittsburgh who forwarded it to the investigatory panel).

No NIMH funds were spent on this project and there are no irregularities or problems with any of the data. Any pertinent issues have been clarified above.

Breuning, S.E., Sisson, L.A., Fultz, S.A., Marshall, T., and Bregman, J.D. Effects of Neuroleptic Drugs on Titrating Delayed Matching-to-Sample Performance of Mentally Retarded Children. Unpublished.

Once Dr. Sprague's concerns/confusion arose and I reviewed the abstract and realized that I had made a mistake, I was able to carefully analyze my professional and personal situation status. I realized that over the previous 6/8 months problems with my personal situation had predominated and that I may have been careless in other areas. Thus, I began carefully reviewing everything. In doing so I became concerned about some aspects of this manuscript. For example, for the first time to I found out that research assistants had not been following the consistent schedule they were suppose to (Dr. Ackles told me this after a conversation he had with one of research assistants). Further, they and students had prepared the methods section and I thought I had better review everything in detail but did not know when I would be able to do so. Thus, this became an abandoned and dead project. With respect to other issues raised a few brief comments. Issues pertaining to Coldwater have been detailed above. The investigatory panel has already established that client records at WPIC are incomplete as several of the Physicians have stated that they often just kept the consent forms. Finally, the statement by research assistants that they did not observe the dramatic effects is ridiculous for two reasons. First, they never raised any concerns; and second, everyone knows that how data look in raw form is typically very different from final format.

Summary. In summary, there is no logical way the investigatory panel can substantiate or conclude that there are any problems other than those I have discussed above. In each case I have or am in the process of taking the necessary and appropriate actions.

Stimulant Studies

In this section I will review work pertaining to grant MH-37449. As described in the investigatory panels report there are three issues which must be addressed. These will be described and dealt with individually below. Of the entire report, these issues are the most difficult for me to deal with. Not because of the type of problem, but rather because of the memories of the problems I experienced in a personal situation and how these problems greatly contributed to the issues I am about to discuss.

1. Year 01 Progress Report for grant MH-37449.

When I interviewed with the investigatory panel I acknowledged that this progress report was misleading and probably inappropriate. However, I most assuredly was not attempting to deceive or mislead any one when it was prepared. As stated, it was prepared during a time period when I had let personal matters totally dominate my professional work and I was not preparing things with the thoroughness and diligence I always had. This was the first progress report that I had ever prepared and I had never received any training at WPIC on the preparation of progress reports and was told by the research office that it is a formality. Best I can recall, the statements about the 65% and 35% subject completion was intended to reflect normative data being collected. In retrospect, the progress report most certainly was not clear on this. The inclusion of previously collected data I thought was appropriate if so identified. It was not so identified. Specific issues pertaining to these data appear below.

While the progress report is incomplete and misleading, I wish to point out that during this year much valuable information was collected. This included, as Dr. Nuffield stated, 12-15 children who received stimulant/placebo trials of some type, nondrug interventions with children having high Conner's scores during the first week of admission and implications for interpretation of subsequent scores, and normative - profiling Conner's scale information for children admitted to an inpatient psychiatric unit. This last issue is most important because it was typically found that the non-drug interventions were highly effective alone. These are what were proposed in the revised continuation proposal. I believe that the precedent clearly exists for such changes to occur into a grant project. I just did not justly reflect this in the progress report. As I told Dr. Kupfer when I left WPIC, I was and still am more than willing to work with WPIC to analyze and prepare all data collected.

Finally, I must point out that this progress report was reviewed by co-investigators and the Research Office (I assume in detail), prior to its submission with no concerns being raised or questions or questions being asked.

2. Continuation Grant

The entire confusion centers around the wrong draft being submitted. The investigatory panel states that when I interviewed with them on November 22, 1985 I gave them "an amended progress report section to the renewal application". This is correct, except that they failed to mention that on February 17, 1984 I submitted this material to the University of Pittsburgh Fact Finding Committee. Further, I discussed this issue with Dr. Kupfer in December of 1983. The investigatory panel seems to have four concerns with the timeliness of this amended report. These are discussed individually below.

a. No evidence that the revised progress report existed prior to the work being called into question by Dr. Sprague.

The first I knew of Dr. Sprague's concerns over any aspect of this report was when I received a copy of a section of a letter he sent to NIMH on 12-20-83. I received a copy of this only on January 17, 1984. I had sent in the letter to NIMH withdrawing this application on December 12, 1983 (a copy of this letter appears in Appendix 4; also, Dr. Gualtieri's written report to the panel states that Drs. Sprague and Kupfer spoke for the first time briefly on 12-12 and in detail on 12-17—both dates after Dr. Kupfer and I had spoken). Further, the withdrawal of this application was only after discussion with Dr. Kupfer at WPIC, Ms. Reatig at NIMH, and Dr. Sprague who I telephoned for instructions on how to withdraw an application. I specifically told Dr. Kupfer that information which could easily be misinterpreted and/or misleading had been submitted and that realistically I was not sure the patient flow and effectiveness of non-drug interventions would support such a project. I only told Ms. Reatig about the issue of patient flow.

When I spoke to Dr. Sprague about this I told him that after the issue with the abstract I began checking everything and found that the wrong information had been included in the application. I said I was going to withdraw it and explain to NIMH what had happened. His only comment was that he thought it would be a good idea. He most certainly did not suggest that he had prior concerns. Our conversation then focused on his instructing me as to how a grant is withdrawn.

Dr. Sprague contends that he reviewed the first draft of the application on the airplane on September 23, 1983 and he immediately became concerned and called together some colleagues to discuss it on September 26, 1983. Yet, on September 29, 1983 Dr. Sprague sent me a letter which states "I found your progress report very interesting, and I have some questions which I will write to you about when I have time". (a copy of this letter appears in Appendix 5). Someone is going to have to explain to me how I was to know Dr. Sprague had concerns based upon this type of correspondence.

Further, Dr. Sprague and I spoke at least several times a month between September and December, 1983. No concerns were ever raised.

My point is merely that Dr. Sprague's concerns were unknown to me. Yet, when I discovered that problems existed with the application I took immediate and appropriate action. No NIMH funds were ever utilized in connection with this application.

Additionally, this first draft of the application had also been reviewed in detail by the WPIC Research Committee and the Research Office with no concerns being expressed to me.

2. That my secretary does not recall typing or submitting a second draft.

To the best I can recall after reading the secretary's statements I agree, I most likely did retype this section myself. Depending on the work load and time frames I often did some of my own typing. Especially if formatting was involved. With respect to her not remembering to submit the revised pages to the Research Office, I am not surprised. If she remembered submitting the revised section we would not be having this discussion now. I am not saying that it was her fault. I recall leaving the revised version on her desk the night before I went out of town. There were instructions on getting it to the Research Office. I suppose anything could have happened to it beyond my leaving it on her desk.

3. That the handwritten revisions were on a paginated copy.

Ms. Kaufman told the investigatory panel that she did not see how I could have made the revisions on a paginated copy since this is done by her staff just prior to mailing and that I was out of town. This is a simple issue to resolve. First, as best I can recall, on Monday or Tuesday, September 24/25, I asked the Research Office (Judy, I think but am not sure) if they could assemble my application in final form so that I could review it before I went out of town. It was prepared early for me and on September 26 I edited it on what would have been a paginated copy. A revised version was then prepared. The date of September 28 in the corner of the revised application merely reflects when it would have been presented to the Research Office. Thus, my being out-of-town for part of the 28th and 29th is no issue. I have not intended to imply that I thought there was an error by the Research Office in this process.

4. Use of previously collected data.

The revised application clearly delineates that analyses of previously collected data were proposed in the new application. It also clearly corrects the problems we have discussed with the Year 01 progress report. It is an honest and concise description of the project.

With respect to the previously collected data, the investigatory panel report suggests that the first time I acknowledged that none of the subjects were from Pittsburgh was during my interview with them in November, 1985. They also repeatedly reference the University Ad Hoc Committee of April/May 1985 which concluded that the majority of subjects were not from the University .

What else could this committee possibly conclude! I told this to Dr. Kupfer in December, 1983 and January, 1984. I told this to the University Fact Finding Committee in February, 1984. I told this to the University Hearing Board in May, 1984.

As I discussed previously, I cannot after this lengthy period of time state the sites of the data collection with any certainty. I have not had the time, money, or interest to retrace these steps. The investigatory panel states that Drs. Koutnik and Regan could not verify that I had collected stimulant data while in Chicago. I never said they could. I said that Dr. Koutnik could verify that I had involvement with some school systems. My interpretation of his interview is that he did indeed verify this. I said that Dr. Regan may or may not be able to. He could not.

Appendix 1 contains a note page from a a May 14-17 Midwestern Association of Behavior Analysis Convention held in Chicago. This page reflects my initial interview with Dr. Nolley. It clearly shows that we had discussed stimulant data that I had collected. Further, Appendix 6 contains a page from the 1978 Midwestern Association of Behavior Analysis Convention Program which shows that I had had stimulant data.

For confidentiality I had not kept any subject or site identifying information. These are the only data I have used knowing that I had not retained the specific subject names and locations. While this will never happen again, I know of no standards that this violates. I used the data because I collected virtually all of it directly and I have all the raw data and summary data. (Technically I do not have this because I gave it all to the panel and it has not been returned).

The investigatory panel states that I gave them a data book which contained no dates and subject identifications, and it did not meet ordinary standards for reporting research data. What I gave them was the complete records, raw and summary data, for each subject. Each sheet was dated and coded. They state that it does not meet standards. Again, what standards! Once I would like the investigatory panel to tell me what standards they are talking about. The panel has never asked me for an explanation of how to read the codes or interpret the dates. Their comments here are very inappropriate.

A few final comments. First, all persons listed on a grant were given a copy of it. Which people are listed on a grant is not the sole determination of the principle investigator at Pittsburgh. This is completely determined in combination with the research office. Dr. Ackles never asked me anything about where data were collected and never expressed any concerns. In fact, in January of 1984 I gave him a copy of all the stimulant data except the rating scales. He has never asked that his name be removed from anything. Second, the only person involved to express concerns appears to be Dr. Poling. As previously discussed, he sent a letter to the editor of the journal where we published some of the stimulant data. His letter says that while he had complete confidence in the data at the time it was published, he could no longer personally vouch that the study was conducted as reported. This was a surprise to me because in our telephone conversation following his interview with the investigatory panel he told me that the interview was very intimidating and that the investigatory panel told him he should write a letter to the journal expressing concern. He told me that he really did not have any concerns but he did not know what to do because he needed grant money. Dr. Poling has never expressed concern to me and I believe that his letter would have never been prepared if it were not for at least tacit pressure of the investigatory panel.

Summary. In summary, some unintentional errors occurred in the Year 01 Progress Report. These were not questioned by any co-investigator or University Official and I did not realize the errors until at least six months later. No final report was ever asked for on this grant. I remain most willing to work with NIMH and WPIC under any scrutiny to review all information and data collected at WPIC and to complete the project.

The wrong draft was accidently submitted for a new grant application. The moment I discovered the error I took all appropriate actions to correct the situation. The revised draft addresses all questions concerning confusions raised by the first draft.

Reviews

Based upon the discussions above, there is no logical way in which the investigatory panel can conclude that published reviews and chapters are unsound and misleading. The panel itself has never questioned the outcome of a single study and there is not an effect reviewed that has not been replicated by myself and others.

Contractual Work Between Illinois and Pittsburgh

I was shocked to see that the investigatory panel totally omitted relevant discussion on the grant subcontract between Dr. Sprague and myself. The panel states that the "there are issues of grant and contract oversight involved rather than scientific contact...although the terms of the contracts appear not to have been met".

It is not at all clear who the investigatory panel is addressing with respect to the oversight. I assume they mean Dr. Sprague and Illinois.

The subcontract called for work on four issues to be carried out at Pittsburgh. These were: (1) examine incidence and severity of dyskinesia with mentally retarded children. (2) Examine the effects of drugs on measures of learning and performance. (3) Examine efficacy of drugs alone and in combination with nondrug therapies. And (4) gather data on the reliability and validity of the RBRS (Resident Behavior Scale). I never had any kind of detailed discussion on these issues with the investigatory panel.

All work on this subcontract was carried out completely from day one of the subcontract. (1) All children entering the Unit received weekly assessment for dyskinesia and other abnormal movements. (2) Virtually all children received regular and systematic assessment of laboratory and applied learning and performance. (3) Systematic and reliable nondrug therapies were in place with all children. And (4) all children were assessed daily with the RBRS and comparative instruments.

At no time did Dr. Sprague ask for any of the data to be sent to him or did he ever ask to see any of the data. No where in the subcontract was it stated that there was an expectation that the data be sent to Dr. Sprague.

All of the data exist and all methods were of the highest caliber. I am more than willing to work through these data with Dr. Sprague. The data are complete and important.

Further, during the investigation the data were offered to the to the investigatory panel if they would sign that in their opinion this would not breach any confidentiality. The panel never provided such a document or again asked to review the data.

The investigatory panel's conclusions with regard to this subcontract are erroneous, based upon no investigation, and personally offensive. If there is an issue here, it most certainly is not with the University of Pittsburgh or me.

Impact of the Research on the Field

The investigatory panel has concluded that the work I have done has impacted on the field of mental retardation with respect to social policies on care and treatment. I hope that this is true. I know that I receive several telephone calls each month from various points around the country expressing that in clinical practice they have found much of what I have reported. However, the merit of research findings and published works can only be assessed over time. With respect to my work or the work of any other if it is correct people will continue to use it in their practice. If not, they won't. This is only known over time. By the way, I have not done any consulting work with the state of Connecticut as reported by the investigatory panel.

Overall Conclusion

At each step of this investigation, beginning with Dr. Sprague's confusion and through the investigatory panel's report, no evidence of any misuse of NIMH funds has been found. There most assuredly were none.

The investigatory panel did conclude that I repeatedly engaged in misleading the results of research. However, the investigation was not complete, did not focus on interviews with appropriate people and/or with appropriate questions, at least tacitly coerced or confused people into making statements which otherwise would have not occurred, and continually used as its base standards which do not exist.

I have never engaged in any misleading research as suggested (and unsupported) by this investigatory panel.

Some mistakes and errors were found. While it is regrettable and embarrassing that these occurred, they exlusively occurred during an eight month period when I had some problems which I let totally dictate my life and I did not adequately supervise or attend to my professional behavior. I am not proud of this, but it occurred. In each case I immediately reported to the proper authorities and proceeded to take appropriate action. I do not know what else is expected of me.

Appendix 1

Notes from May 14-17, 1977 Midwestern Association of Behavior Analysis Convention Program Booklet.

MABA

third annual convention

midwestern association of behavior analysis

may 14-17, 1977

blackstone hotel

chicago, illinois

An easy to use procedure for NOTES

Emily Koenig
1204 Monroe
Evanston, Ill. 60202

[illegible]
Dept. Human Development
University of Kansas
[illegible]

Met Dave Knolly. As
nee by Silver. Can manage work like very
at Sopeen center. Dave seems work
sad guy. He says cont & drug wd tol.
(we talked about FQ, IQ + drug will be no prob.
stuff like RC, workshop etc) work is possible.
Also said animal work - showed him some med. di:
Dave from work, wd FR data. He thought ü
drug workshop! FQ, He'll work with me on
should be pub. He really liked
same if he can help. He to Dave?
ritalin stuff. He intro me to [illegible]
[illegible] said yes no prob -- even wd
[illegible] to call To visit
[illegible] view.

Appendix 2

Tom Gualtieri's analyses of the tardive dyskinesia data.

		B	4	16	52	80				
	1	✓	✓	✓	✓	✓	TD			
	2						[illegible]	10		
	3		✓	✓	✓	✓	TD			
	4		✓	✓	✓	✓	TD			
	5	✓	✓	✓	✓	✓	TD			
	6							10		
	7								WSX	
	8		✓							WD
	9		✓	✓	✓	✓	TD			
	10							10		
	11		✓	✓	✓	✓	TD			
*	12		✓	✓						
	13		✓	✓	✓	✓	TD			
	14							10		
	15		✓	✓	✓	✓	TD			
	16							10		
	17		✓	✓	✓	✓	TD			
	18		✓							WD
	19							10		
	20		✓							
	21								WSX	
*	22		✓	✓						
	23							10		
	24							10		
*	25		✓	✓						
	26		✓	✓	✓	✓	TD			
	27		✓							WI
	28							10		
	29							10		
	30	✓	✓	✓	✓	✓	TD			
*	31		✓	✓	✓					
	32		✓	✓	✓	✓	TD			
*	33		✓	✓						
	34		✓							WD
	35		✓	✓	✓	✓	TD			
	36							10		
*	37		✓	✓						
	38		✓	✓	✓	✓	TD			
	39							10		
	40		✓	✓	✓	✓	TD			
	41		✓							
	42		✓	✓	✓	✓	TD			
	43							10		
*	44		✓	✓						
	45							10		
	46							10		
	47							10		
*	48		✓	✓						

		B	4	16	52	80		
*	49		✓	✓				
*	50		✓	✓				
	51							
	52							1010
*	53		✓	✓				
	54	✓	✓	✓	✓	✓	TD	
	55							10
*	56		✓	✓				
	57		✓	✓	✓	✓	TD	
12	57	4	36	30	18	18	18	19

	N	%A	AGE	%♂	IQ	% THD	DOSE	M/K	dur
NO PROBLEMS	19	42	25.5 ± 14.9	53	38 ± 11.4	42	721.1 ± 398	16.3 ± 17.1	4.04 ± 2
ITHDRAWAL PX	20	40	25.7 ± 13.4	50	41.6 ± 15.3	40	710 ± 304.6	13.3 ± 6.3	4.1 ± 2
MILD TD	3	67	27.7 ± 6.0	33	35.0 ± 18.2	0	666.7 ± 115.5	11.6 ± 2.7	4.1 ±
M-S TD	15	53	29.7 ± 14.7	47	41.5 ± 18.5	73	623.3 ± 216.2	10.4 ± 3.6	4.4 ± 3

Ō WPx	At	All	IQ	drug		dose	dur	m/k
2	18	F	57	T		1200	4.2	23.1
6	14	M	49	T		400	3.7	8.8
10	19	M	56	T		400	3.2	9.2
14	25	M	34	H	12	600	2.1	8
16	17	F	27	H	12	600	0.9	13.5
19	49	F	34	T		400	12.9	7.1
23	18	M	26	C		600	2.2	7.5
24	24	M	49	T		300	6.2	6.1
28	18	M	34	M	400	800	4.4	10
29	13	M	42	C	1200	1200	1.6	25.5
36	17	F	41	C		500	7.4	9.2
39	19	F	19	T	n	700	3.1	12.7
43	22	M	39	H	30	1500	6.4	80
45	40	M	29	H	12	600	2.1	20
46	71	F	21	C	800	800	6.3	8.7
47	31	F	27	T	L	400	1.3	6.7
51	13	M	53	C		900	1.4	15.0
52	39	F	40	T		200	4.8	6.3
55	17	F	51	H	32	1600	2.6	31.5
(19)	25.5 ± 14.9	10 M F 9	38.0 ± 11.4	T 8 H 5 C 5 M 1		721.1 ± 398.0	4.04 ± 2.9	16.3 ± 17.1

other WPx, ō TD

SUBJ	A/G	AGe	sex	IQ	meD	Dose	m/k	doe
7	A	41	M	58	C	400	6.4	3
8	A	46	M	23	H	800	9.5	12.3
12	A	23	F	27	C	1050	21.2	1.6
18	A	14	M	28	T	900	21.6	2.2
20	A	13	F	61	T	500	13.1	1.9
21	A	16	M	26	C	600	15.2	4.6
22	A	56	M	18	T	400	6.2	2.7
25	A	23	F	52	T	750	15.3	3.2
27 ✓	G	13	F	34	T	400	9.3	1.1
31 ✓	G	12	M	27	H	900	25.5	3.1
33 ✓	G	21	F	56	H	400	7.5	2.4
34 ✓	G	34	F	69	H	1600	28	5.6
37 ✓	G	20	M	50	H	800	9.5	4.6
[illegible]	[illegible]							
41	G	19	F	23	T	500	9.1	2.6
44	G	26	M	47	T	900	11.3	8.7
48	G	37	F	46	M	900	14.1	4.2
49	G	14	F	54	H	400	12.5	1.9
50	G	49	F	57	M	800	10.3	7.3
53	G	15	M	34	H	400	7.5	3.1
56	G	22	M	42	T	800	14.3	6.1
N=20	A = 8	25.7	M=10	41.6	T 8	710.0	13.3	4.1
	G = 12	13.4	F=10	15.3	H 7	±309.6	6.3	2.8
					C 3			
					M 2			

other WPx, ō TD

SUBJ	A/G	AGE	sex	IQ	med	dose	m/k	dur
7	A	41	M	58	C	400	6.4	3
8	A	46	M	23	H	800	9.5	12.3
12	A	23	F	27	C	1050	21.2	1.6
18	A	14	M	28	T	900	21.6	2.2
20	A	13	F	61	T	500	13.1	1.9
21	A	16	M	26	C	600	15.2	4.6
22	A	56	M	18	T	400	6.2	2.7
25	A	23	F	52	T	750	15.3	3.2
27 ✓	G	13	F	34	T	400	9.3	1.1
31 ✓	G	12	M	27	H	900	25.5	3.1
33 ✓	G	21	F	56	H	400	7.5	2.4
34 ✓	G	34	F	69	H	1600	28	5.6
37 ✓	G	20	M	50	H	800	9.5	4.6
41	G	19	F	23	T	500	9.1	2.6
44	G	26	M	47	T	900	11.3	8.7
48	G	37	F	46	M	900	14.1	4.2
49	G	14	F	54	H	400	12.5	1.9
50	G	49	F	57	M	800	10.3	7.3
53	G	15	M	34	H	400	7.5	3.1
56	G	22	M	42	T	800	14.3	6.1
N=20	A=8	25.7	M=10	41.6	T 8	710.0	13.3	4.1
	G=12	13.4	F=10	15.3	H 7	±309.6	6.3	2.8
					C 3			
					M 2			

TD- MILD		MO	DRUG	AGE	SEX	IQ	DOSE	DUR	M/K
SUBJ	A/G								
1	A	X	C	34	M	45	600	6.4	12.
11	A		H	22	F	14	800	3.2	13.5
38	G		C	27	F	46	600	2.8	8.5
N=3	2A 1G	1	T=0 H=1 C=2	27.7 6.0	M=1 F=2	35.0 ±18.2	666.7 ±115.5	4.1 ±2.0	11.6 2.7

TD: M-5

SUBG	A/G	MO	AGE	SEX	IQ	MED	dose	m/k	dur
3	A		19	M	74	T	500	6.8	12.
4	A		32	M	35	T	750	11.9	1.6
5	A	X	25	F	19	C	600	12.2	5.4
9	A		25	F	63	T	800	14.5	8.3
13	A		28	F	37	T	300	5.9	3.4
15	A		17	M	47	H	300	4.5	2.7
17	A		24	M	27	T	1050	14.7	4.1
26	A		41	F	21	T	900	15.1	1.3
30	G	X	61	M	61	T	500	7.1	3.7
32	G		17	F	29	T	600	13.9	4.2
35	G		20	M	62	T	800	9.1	1.3
40	G		36	F	23	T	450	7.8	7.2
42	G		18	M	36	C	750	14.7	1.6
54	G	X	62	F	26	C	450	8.2	6.
57	G		21	F	63	T	600	10.2	1.7
N=15	A=8 G=7	3	29.7 ±14.7	M= 7 F= 8	41.5 ±18.5	T 11 H 1 C 3	623.3 216.2	10.4 3.6	4.4 3.1

A/

	WD	TD -MO	TD -WD	WSx	$\bar{O}$	TD c̄ more Sx 1st 16 wks
1		1				
2					0	
3			2			+
4			2			+
5		2		1		+
6					0	
7				2		
8	2					
9			2	2		+
10					0	
11			1			+
12	2			1		
13			2			+
14					0	
15			2			+
16					0	
17			2			+
18	2			1		
19					0	
20	2					
21				1		
22	1					
23					0	
24					0	
25	1			1		
26			2	1		
N 26	6	2	8	8	8	8
MILD (1)	2	1	1	6		
MOD. SEV (2)	4	1	7	2		

		WD	TD -MO	TD -WD	WSx	$\bar{o}$	TD ē >Sx durin 1st 16 wks
	27	2					
	28					0	
	29					0	
	30		2	[illegible]			+
	31	2			1		
	32			2	1		
	33	2			1		
	34	1			1		
	35			2			+
	36					0	
	37	1					
	38			1			+
	39					0	
	40			2	2		
	41				1		
	42			2			+
	43					0	
	44	1					
	45					0	
	46					0	
	47					0	
	48	1			1		
	49	2					
	50	1					
	51					0	
	52					0	
	53	1	[illegible]		1		
	54		2				
	55					0	
	56	1					
	57			2	1		
N	31	11	2	6	9	11	4
MILD		7	0	1	8		
MOD.SEV		4	2	5	1		

TD

									MD
1		34	M	45	C		600	6.4	X
3	*	19	M	74	T		500	12.4	
4	*	32	M	35	T		750	1.6	
5	*	25	F	19	C		600	5.4	X
9	*	25	F	63	T		800	8.3	
11		22	F	14	H	16	800	3.2	
13	*	28	F	37	T	300	300	3.4	
15	*	17	M	47	H	6	300	2.7	
17	*	24	M	27	T		1050	4.1	
26	*	41	F	21	T		900	1.3	
30	*	61	M	61	T		500	3.7	X
32	*	17	F	29	T		600	4.2	
35	*	20	M	62	T		800	1.3	
38		27	F	46	C		600	2.8	
40	*	36	F	23	T		450	7.2	
42	*	18	M	36	C		750	1.6	
54		62	F	26	C	450	450	6.4	X
57	*	21	F	63	T		600	1.7	
n = 18		29.9 ± 13.8	8 M 10 F	39.1 ± 17.7	C = 5 T = 11 H = 2		632.4 ± 206.9		

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WSX

5	25	F	19	CPZ	600	600	5.4
7	41	M	58	CPZ	400	400	3.0
9	25	F	63	THD	400	400	8.3
12	23	F	27	CPZ	1050	1050	1.6
18	14	M	28	THD	900	900	2.2
21	16	M	26	CPZ	600	600	4.6
25	23	F	52	THD	750	750	3.2
26	41	F	21	THD	900	900	1.3
31	12	M	27	HDL	18	900	3.1
32	17	F	29	THD	600	600	4.2
33	21	F	56	HDL	8	400	2.4
34	34	F	69	HDL	32	1600	5.6
40	36	F	23	THD	450	450	7.2
41	19	F	23	THD	500	500	2.6
48	37	F	46	meso	450	900	4.2
53	15	M	34	HDL	8	400	3.1
57	21	F	63	THD	600	600	1.7
	24.7 ±9.6	5 M 12 F	39.1 ±17.4	CPZ 4 THD 8 HDL 4 meso 1		702.9 ±316.	

WD-2

	Age	sex	IQ	drug	dose	equivs CPZ	duration
8	46	M	23	HDL	16	800	12.3
12	23	F	27	CPZ	1050	1050	1.6
18	14	M	28	THD	900	900	2.2
20	13	F	61	THD	500	500	1.9
27	13	F	34	THD	400	400	1.1
31	12	M	27	HDL	18	900	3.1
33	21	F	56	HDL	8	400	2.4
49	14	F	54	HDL	8	400	1.9
	19.5 ± 11.5	3M 5F		3 THD 4 HDL 1 CPZ			

WD-1

A	22	56	M	18	THD	400	400	2.7
A	25	23	F	52	THD	750	750	3.2
	34	34	F	69	HDL	32	1600	2.4
	37	20	M	50	HDL	16	800	4.6
	44	26	M	47	THD	900	900	8.7
	48	37	F	46	meso	450	900	4.2
	50	49	F	57	meso	400	800	7.3
	53	15	M	34	HDL	8	400	3.1
	56	22	M	42	THD	800	800	6.1
			5M 4F		4 THD 3 HDL 2 meso			
		25.8 ± 13.8	8M 9F	42.6 ± 14.9	7 THD 7 HDL 1 CPZ 2 meso		747.1 ± 315.0	

		ABRUPT		GRADUAL		TOTAL	
N		26		31		57	
WD		6		11		17	
	MILD		2		7		9
	MOD·SEV		4		4		8
TD·MO		2		2		4	
	MILD		1		0		1
	MOD·SEV		1		2		3
TD·WD		8		6		14	
	MILD		1		1		2
	MOD·SEV		7		5		12
WSx		8		9		17	
	MILD		6		8		14
	MOD·SEV		2		1		3
D c̄ >Sev Sx 1ST 16 WKS		8		4		12	
No problems		8		11		19	
TD (MO OR WD)		10		8		18	
	MILD		2		1		3
	MOD·SEV		8		7		15
YSK: LHT		16		18		34	
	MILD		11		16		27
	MOD·SEV		5		2		7
YSK: LIP-FACE		16		14		30	
	MILD		9		9		18
	MOD·SEV		7		5		12
YSK: TONGUE		15		19		34	
	MILD		4		9		13
	MOD·SEV		11		10		21

LHT C·A Gc myoclonic

1 = mild
2 = mod/sev

	B	1	4	8	16	52	80
1							
3	0	2	1	0	1	1	2
4	0	1	2	2	2	2	2
5	0	1	2	0	0	0	0
8	0	1	2	2	0	0	0
9	0	1	1	1	1	0	0
11	0	1	1	1	1	0	0
12	0	1	1	1	1	0	0
13	0	1	~~2~~ 1	2	2	2	2
15	0	1	1	2	1	0	0
17	0	1	2	2	2	2	2
18	0	1	1	1	0	0	0
20	0	1	2	1	0	0	0
22	0	1	1	1	0	0	0
25	0	1	1	1	1	0	0
26	0	2	1	1	1	1	1
27	0	1	1	1	0	0	0
30	0	2	2	2	0	0	0
31	0	1	1	1	1	0	0
32	0	2	2	2	2	2	1
33	0	1	1	1	0	0	0
34	0	1	1	0	0	0	0
35	0	1	1	1	1	0	0
37	0	1	1	1	1	0	0
38	0	0	1	1	1	0	0
40	0	1	1	2	1	2	2
42	0	1	1	1	0	0	0
44	0	1	1	1	0	0	0
48	0	1	1	1	1	0	0
49	0	0	1	1	0	0	0
53	0	1	1	1	0	0	0
54	0	1	1	1	1	1	1
56	0	1	1	1	1	0	0
57	0	1	1	1	2	2	2
33	0	31	33	30	20	9	9
MOD-SEV	0	4	7	7	5	6	6
16	0	16 2	16 5	14 5	11 3	5 3	5 4
18	0	16 2	18 2	17 2	10 2	4 3	4 2
X̄ SEV	0	1.13	1.21	1.23	1.25	1.67	1.67

LIP. FACE

	SUBJ	B	1	4	8	16	52	80
A	1	1	1	2	2	1	1	1
	3	0	1	1	1	0	0	0
	4	0	1	2	2	0	0	0
	5	1	1	2	2	2	2	2
	8	0	1	1	1	0	0	0
	9	0	2	2	2	2	2	2
	11	0	1	1	1	1	1	1
	12	0	1	2	2	1	0	0
	13	0	1	1	1	0	0	0
	15	0	2	2	2	2	2	2
	17	0	1	1	1	0	0	0
	18	0	1	1	0	0	0	0
	20	0	2	2	1	0	0	0
	22	0	1	1	1	1	0	0
	25	0	1	1	1	0	0	0
	26	0	1	1	1	1	1	1
1	27	0	1	1	1	0	0	0
	30	1	2	2	2	2	2	2
	31	0	2	2	1	0	0	0
	32	0	1	2	2	2	2	2
	34	0	0	1	0	0	0	0
	38	0	0	1	1	1	1	1
	40	0	1	2	2	2	2	2
	42	0	1	1	1	1	1	1
	44	0	0	1	1	1	0	0
	48	0	0	1	1	0	0	0
	50	0	0	1	1	0	0	0
	54	1	1	2	2	2	2	2
	56	0	0	1	1	0	0	0
	57	0	1	1	2	1	0	0
N (27)	20	4	24	30	28	17	12	12
N MOD-SEV		0	5	12	11	7	7	7
N MOD-SEV	16 0.62	2 0	16 2	16 7	15 6	8 3	6 3	6 3
	14 0.45	2 0	14 2	14 5	13 5	8 4	6 4	6 4
$\bar{x}$ SEV		1.0	1.21	1.4	1.39	1.41	1.58	1.58

TONGUE

	SUBJS	B	1	4	8	16	52	80
A	1	1	1	2	2	1	1	1
	3	0	1	1	2	0	0	0
	4	0	1	2	2	0	0	0
	5	1	1	2	2	2	2	2
	8	0	1	2	2	0	0	0
	9	0	2	2	2	2	2	2
	11	0	1	2	2	1	1	1
	12	0	1	2	2	1	0	0
	13	0	1	1	1	0	0	0
	17	0	1	1	1	0	0	0
	18	0	1	2	2	0	0	0
	20	0	2	2	1	0	0	0
	22	0	1	1	1	1	0	0
	25	0	2	2	1	1	0	0
15	26	0	1	2	2	2	2	2
	27	0	1	2	1	0	0	0
	30	2	2	2	2	2	2	2
	31	0	2	2	1	0	0	0
	32	0	1	2	2	2	2	2
	33	0	1	2	2	1	0	0
	34	0	0	1	0	0	0	0
	35	0	1	2	2	2	2	2
	37	0	1	1	1	1	0	0
	38	0	0	1	1	1	1	1
	40	0	1	2	2	2	2	2
	42	0	1	1	1	1	1	1
	44	0	1	1	1	1	0	0
	48	0	0	1	1	1	0	0
	49	0	1	2	2	1	0	0
	50	0	1	1	1	1	0	0
	53	0	1	1	2	1	0	0
	54	1	1	2	2	2	2	2
	56	0	1	1	1	1	0	0
19	57	0	1	2	2	2	2	2
34 m-s		4 1	31 5	34 21	33 19	24 9	13 9	13 9
15		2 0	15 3	15 11	15 10	8 3	5 3	5 3
19		2 1	16 2	19 10	18 9	16 6	8 6	8 6
X̄ SEV		1.25	1.16	1.62	1.58	1.38	1.69	1.69

[illegible], Anorexia, Vom, Wt loss: WSX

	SUBJ	B	1	4	8	16	52	80
A	5	0	1	1	0	0	0	0
	7	0	2	2	0	0	0	0
	9	0	1	1	2	0	0	0
	12	0	1	1	2	0	0	0
	18	0	1	1	0	0	0	0
	21	0	1	1	1	0	0	0
	25	0	1	1	1	0	0	0
	26	0	1	1	0	0	0	0
N	8	0	8	8	3	0	0	0
mod·sev		0	1	1	1	0	0	0
♀	31	0	1	1	0	0	0	0
	32	0	1	1	0	0	0	0
	33	0	1	1	0	0	0	0
	34	0	1	0	0	0	0	0
	40	0	2	2	2	0	0	0
	41	0	1	1	1	0	0	0
	48	0	1	0	0	0	0	0
	53	0	1	1	0	0	0	0
	57	0	1	1	1	1	0	0
N	9	0	9	7	3	1	0	0
mod·sev		0	1	1	1	0	0	0
TOTAL N	17	0	17	15	6	1	0	0
mod·sev		0	2	2	2	0	0	0
$\bar{X}$ sev		0	1.11	1.14	1.33	1	0	0

POSTURING	B	1	4	8	16	52	80
12	0	0	1	1	0	0	0
27	0	1	0	0	0	0	0

ATAXIA							
27	0	1	2	0	0	0	0

No: terminal tremor, hypertonia, euphoria or elation.

	B	1	4	8	16	52	8
ALL DYSKINETIC MOVEMENTS							
TONGUE	.07	.54	.60	.58	.42	.23	.2
LIPS, FACE	.07	.42	.53	.49	.30	.21	.2
LIMBS, HEAD, TRUNK	0	.54	.58	.53	.35	.16	.1
MILD MOVEMENTS							
TONGUE	.05	.46	.23	.25	.26	.07	.07
LIPS, FACE	.07	.33	.32	.30	.18	.09	.0
LIMBS, HEAD, TRUNK	0	.30	.46	.40	.26	.05	.0
MOD-SEV MVS							
TONGUE	.02	.09	.37	.33	.16	.16	.16
LIPS, FACE	0	.09	.21	.19	.12	.12	.12
LIMBS, HEAD, TRUNK	0	.07	.12	.12	.09	.11	.11

		B	4		16		80
All	TON	4	34	→ 10 →	24	− 11 −	13
	LF	4	30	− 13	17	− 5 −	12
	HLT	0	33	− 13	20	− 11 −	9
MILD	TON	3	13	−+2	15	-9	4
	L.F	4	18	-8	10	-5	5
	HLT	0	26	-11	15	-12	3
M-S	TON	1	21	-12	9	0	9
	L.F	0	12	-5	7	0	7
	HLT	0	7	-2	5	+1	6

		TOTAL GROUP	NO PROBLEMS	WSx	WD	TD
N		57	19 (0.33)	17 (0.30)	17 (0.30)	17 (0.
AGE		25.7 ±12.6	25.5 ±14.9	24.7 ±9.6	25.8 ±13.8	29.9 ±13
ex	M	28 (0.49)	10 (0.53)	5 (0.29)	8 (0.47)	8 (0.
	F	29 (0.51)	9 (0.47)	12 (0.71)	9 (0.53)	9 (0
Q		40.4 ±14.8	38.0 ±11.4	39.1 ±17.4	42.6 ±14.9	39.1 ±17.
EDS	C	13 (0.23)	5 (0.26)	4 (0.24)	1 (0.06)	5 (0.
	T	27 (0.47)	8 (0.42)	8 (0.47)	7 (0.41)	10 (0.
	H	14 (0.25)	5 (0.26)	4 (0.24)	7 (0.41)	2 (0
	M	3 (0.05)	1 (0.05)	1 (0.06)	2 (0.12)	0 (
DOSE		685.58	721.1 ±398.0	702.9 ±316.0	747.1 ±315	632. ±206

AGE $\bar{x}$ = 25.7 ± 12.6 SD

range 12-71 yo

distrib:

12-19	23
20-29	17
30-39	7
40-49	6
50-59	1
60-69	2
70→79	1

IQ

$\bar{x}$ = 40.4 ± 14.8

range = 14→74

distrib

B	1
mildr	10
modr	18
sev	19
prof	9

sex

♀	29
♂	28

meds

HDL	N = 14	$\bar{x}$ = 15.9	± 9.1	
CPZ	13	696	± 235.8	795
THD	27	607.4	± 251.8	
meso	3	416.7	± 28.9	

ration Rx: @ least 4.2 yrs ($\bar{x}$ ± 2.8)

LIP FACE

@ 4 wks, 30 dysk
18 mild
12 M-S

MILD	0	𝍸 𝍸 ||||	14
	1	||||	4
	2		0
M-S	0	||||	4
	1	|	1
	2	|||||||	7

mild 18 → 4 P
M-S 12 → 8 P

	P	ō P	
M-S	8	4	12
MILD	4	14	18
	12	18	30

$\chi^2 = 5.93$

$P < .025$

Tongue

34 had dysk @ 4 wks
21 M-S*
13 mild

M-S	0	𝍸 𝍸	10
	1	||	2
	2	𝍸 ||||	9
MILD	0	𝍸 𝍸 |	11
	1	||	2
	2		0

MILD 13 → 2 P
M-S 21 → 11 P

	P	ō P	
M-S	2	11	13
MILD	11	10	21
	13	21	34

$\chi^2 = 4.6$
$P < .05$

HT

CA on myoclonic

@ 4 wks
33 had dysk
26 mild
7 M-S

26 mild			
0	~~[illegible]~~	~~||||~~ ~~||||~~ ~~||||~~ ~~||||~~	20
1	[illegible]	||	2
2	[illegible]	||||	4

7 M-S		
0	||||	4
1	|	1
2	||	2

26 → 6 persistent
7 → 3 persistent

	P	ō P	
mild	6	20	26
M-S	3	4	7
	9	24	33

$\chi^2 = 1.09$

P >.20

ABLE II : OUTCOME

	N	AGE (YEARS)	SEX	IQ	AGE TREATMENT BEGAN (YEARS)	DURATION OF TREATMENT (MONTHS)	TOTAL NEUROLEPTIC DOSE (CPZ EQUIVS)	TH PRIN NEUR
O WITHDRAWAL PROBLEMS	12	14.8 ± 7.3	M = 11 F = 1	28.5 ± 13.8	7.6 ± 3.5	75 ± 64.4	301.4 ± 272.7	THD = (83
THDRAWAL PROBLEMS, D TARDIVE DYSKINESIA	13	15.8 ± 6.1	M = 9 F = 4	35.6 ± 15.7	9.1 ± 4.3	78.4 ± 49.7	393 ± 946.7	THD = (69
ILD TD	5	19 ± 10.9	M = 4 F = 1	42.6 ± 23.1	13.2 ± 7.9	70.6 ± 42.5	273.3 ± 224.3	THD = (100
OD-SEV TD	8	32.5 ± 9.3	M = 4 F = 4	21 ± 6.7	17.1 ± 7.1	188.4 ± 63.5	3609.4 ± 3619.8	THD = (50%
D: MAINTENANCE ONSET	3	35.3 ± 7.5	M = 2 F = 1	22.0 ± 5.2	16.5 ± 5.7	229.3 ± 35.9	5375.7 ± 5248.5	THD = 1 (33%
: PERSISTENT	5	33.8 ± 5.8	M = 2 F = 3	23.2 ± 4.0	15.1 ± 4.5	225.4 ± 26.0	5221.6 ± 3761.5	THD = 2 (40%)

Appendix 3

Additional analyses of the tardive dyskinesia data by Tom Gualtieri.

THE UNIVERSITY OF NORTH CAROLINA
AT
CHAPEL HILL

Division of Health Affairs
The School of Medicine
Department of Psychiatry

March 19, 1981

Steve Breuning
University of Pittsburgh School of Medicine
Department of Psychiatry
3811 O'Hara Street
Pittsburgh, Pa. 15261

Dear Steve:

This is a plot of the time course of the dyskinesias and withdrawal symptoms from your Coldwater data. I think they are very interesting graphs, and I am making them into slides.

As I continue to work on your data, I'll let you know what comes up. I think it is extremely interesting and important.

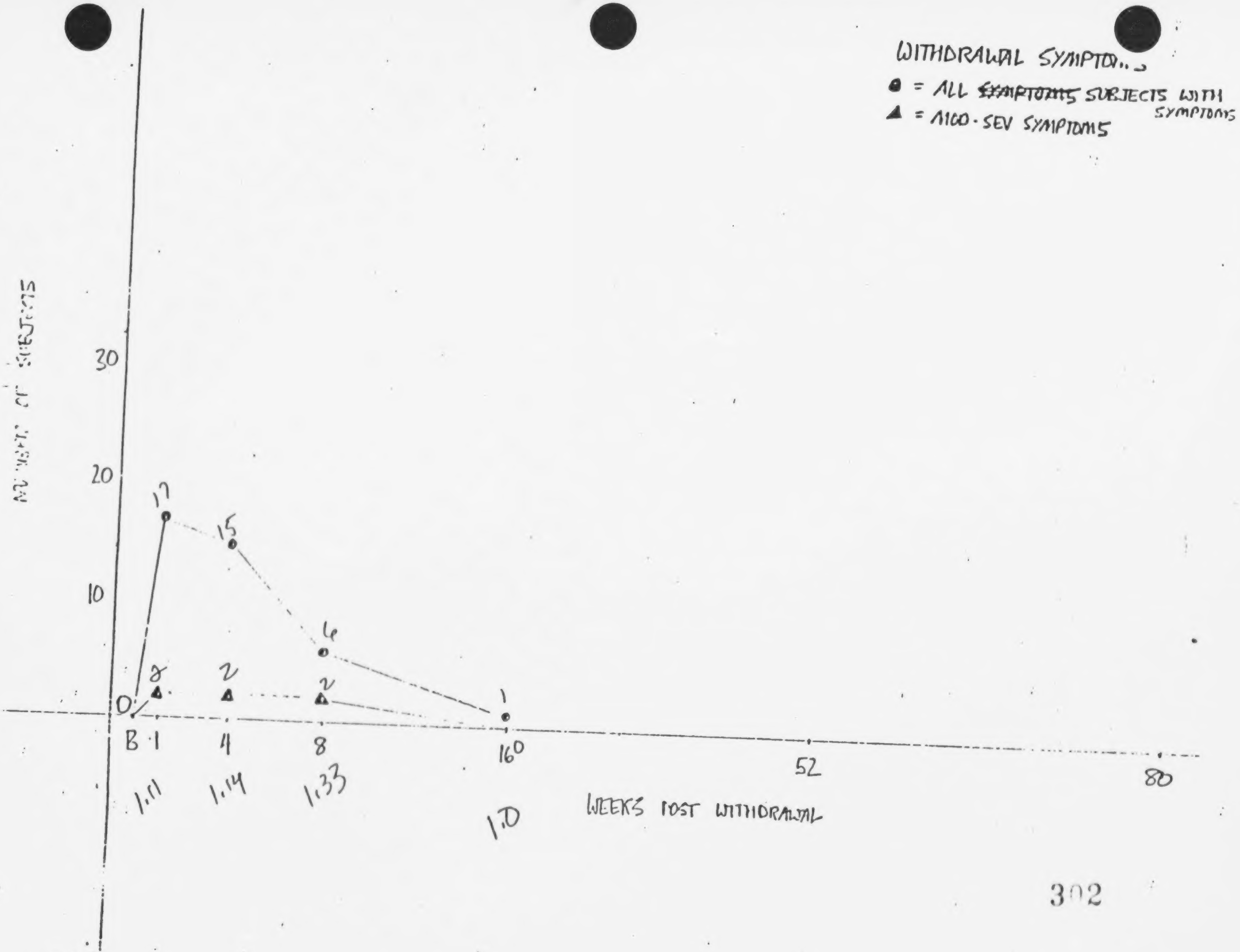
I enjoyed your visit thoroughly. I thought it was incredibly productive. I look forward to seeing you in Key Biscayne.

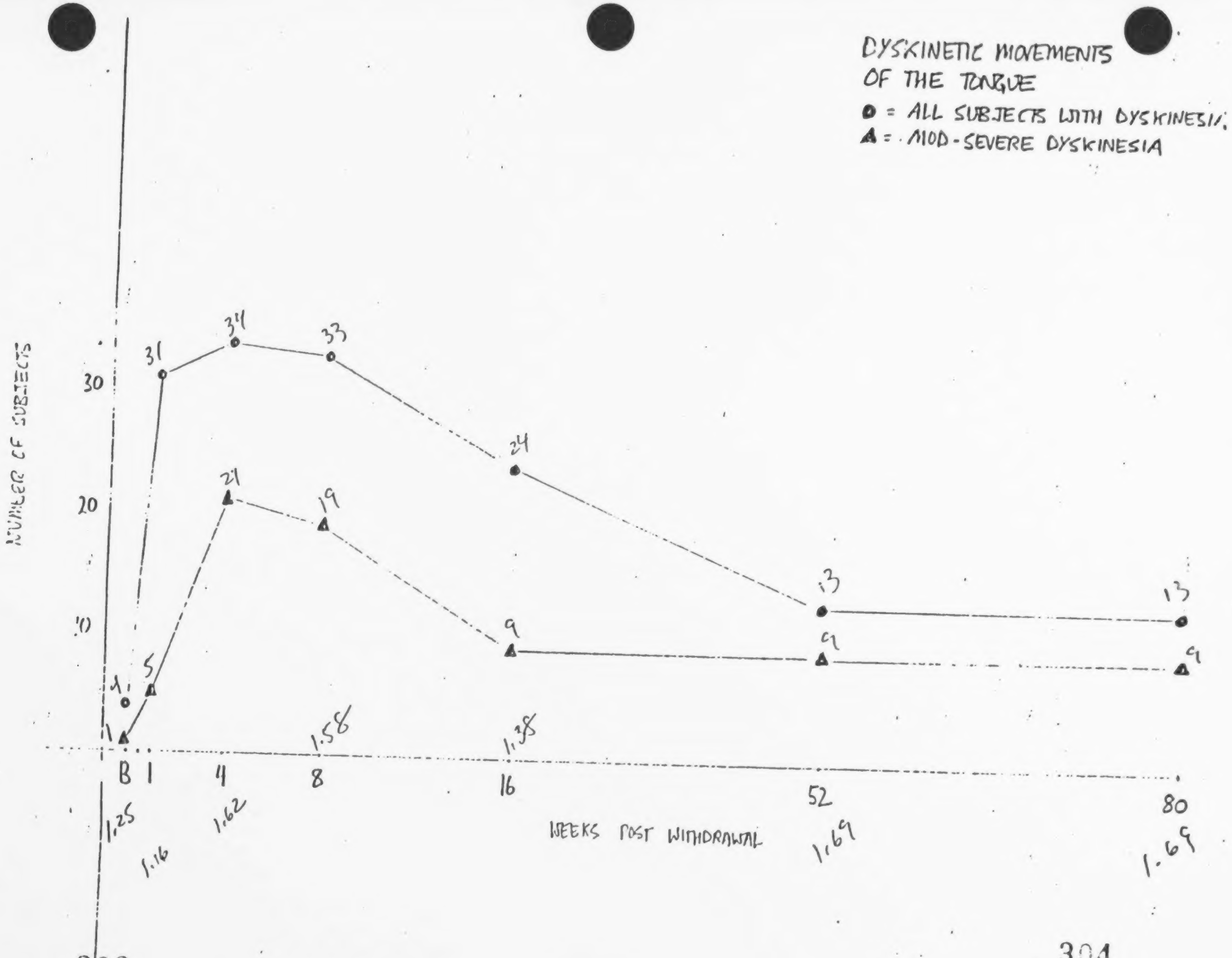
Sincerely,

Tom

C. Thomas Gualtieri, M.D.
Assistant Professor

CTG:jh
Enclosure


WITHDRAWAL SYMPTOMS
● = ALL ~~SYMPTOMS~~ SUBJECTS WITH SYMPTOMS
▲ = MOD · SEV SYMPTOMS
NUMBER OF SUBJECTS
30
20
10
17
15
6
1
0
2
2
2
0
B
1
4
8
16
52
80
1.11
1.14
1.33
1.0
WEEKS POST WITHDRAWAL


DYSKINETIC MOVEMENTS
OF THE TONGUE
● = ALL SUBJECTS WITH DYSKINESIA
▲ = MOD-SEVERE DYSKINESIA
NUMBER OF SUBJECTS
30
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WEEKS POST WITHDRAWAL
B
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4
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34
33
24
13
13
1
5
21
19
9
9
9
1.25
1.16
1.62
1.58
1.38
1.69
1.69

Appendix 4

December 12 letter withdrawing the grant renewal application.

University of Pittsburgh

WESTERN PSYCHIATRIC INSTITUTE AND CLINIC
School of Medicine Department of Psychiatry
Division of Child and Adolescent Psychiatry

December 12, 1983

Richard Marcus, Ph.D.
Executive Secretary
Pharmacological, Biological, and
Physical Treatments Subcommittee (TDAB)
Parklawn Building, Room 9C-18
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Marcus:

I wish to inform you that I am withdrawing my grant application 2 R01 MH37449-03 (Stimulant Drug Use with Mentally Retarded Children), from review at this time. I have discussed this with Natalie Reatig, the project officer, and with Dr. David Kupfer, my department chairman, and they are in agreement with my decision. For your information, the primary reason for my withdrawal of the application is that the patient population I work with may be undergoing a change in the near future and I am not sure whether there would be a sufficient number of clients for both this project and my Drug/Behavior Therapy application which is currently under review. Once I know the status of the other application (Drug/Behavior Therapy) and my clinical population, I will be able to better assess this application. Hopefully, I will be able to re-submit this application in the near future.

Thank you for your immediate attention to this matter and I apologize for any inconvenience.

Sincerely,

Stephen E. Breuning, Ph.D.
Assistant Professor of
Child Psychiatry
University of Pittsburgh
School of Medicine

SEB:WD

cc: Dr. David Kupfer
Ms. Natalie Reatig

3811 O'HARA STREET, PITTSBURGH, PA 15213 (412) 624-2331

Appendix 5

Dr. Sprague's letter to me on September 29, 1983.

University of Illinois
at Urbana-Champaign

Institute for Child Behavior
and Development

51 Gerty Drive
Champaign
Illinois 61820

Graduate College

September 29, 1983

Dr. Stephen E. Breuning
Department of Psychiatry
Western Pennsylvania Psychiatric
Clinic and Institute
University of Pittsburgh
3811 O'Hara Street
Pittsburgh, PA 15261

Dear Steve:

As a follow up of our telephone conversation of September 28, 1983, I will request our Contracts Office to increase the Pittsburgh subcontract for the 1983-84 on MH 1832206-05 from the current $22,645 to $24,558.

I found your Progress Report very interesting, and I have some questions which I will write to you about when I have time.

Sincerely,

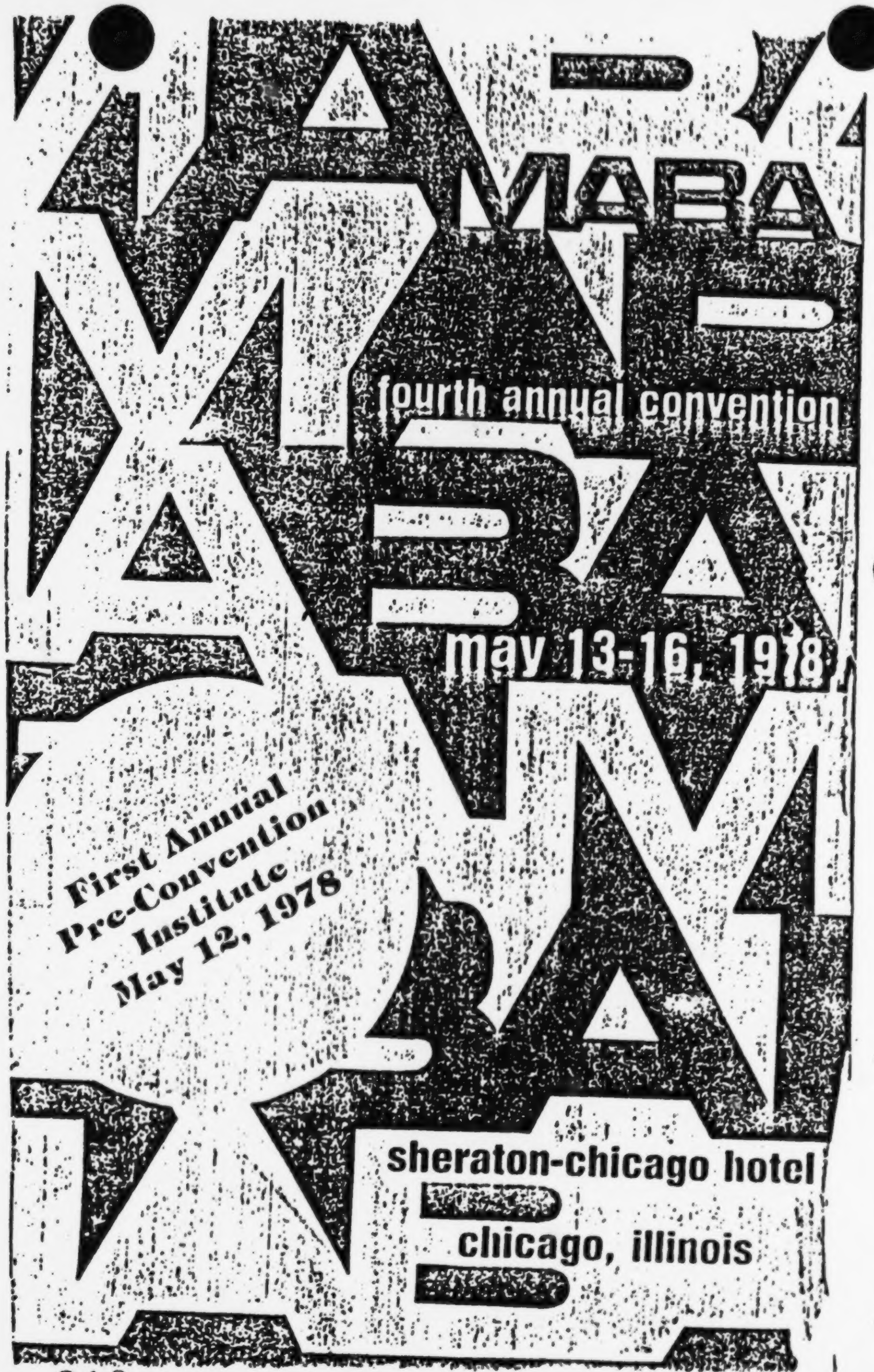
Bob

Robert L. Sprague, Ph.D.
Director

RLS/jm

Appendix 6

Page from May 13-16 Midwestern Association of Behavior Analysis Convention Program Booklet.



10:00–11:00 / BOULEVARD ROOM
Invited Address 60 / Ellen P. Reese (Mount Holyoke College)
"Alternative Evaluations of Students' Possessive Plural Repertoires: When Did *You* (Instructor) Last Take a Quiz?"
Chair: Beth Sulzer-Azaroff (University of Massachusetts)

10:00–11:00 / TROPICAL ROOM
Inivted Address 61 / Norman Hymowitz (New Jersey Medical School)
"The Multiple Risk Factor Intervention Trial"
Chair: Eliot Shimoff (University of Maryland, Baltimore County)

10:00–11:00 / TOWER HALL (Upper A)
Meeting / Special Interest Group: Teachers Teaching Courses Using B. F. Skinner's Book, *Verbal Behavior* (Or, Those Who Would Like To)
Moderator: W. Scott Wood (Drake University)

10:00–12:00 / KINGSTON ROOM
Symposium 48 / Behavioral Alternatives to Drug Control
Chair: Frederick P. Gault (Western Michigan University)
Discussant: Galen Alessi (Western Michigan University)
Participants:
William Hampstead (Western Michigan University) "Effects of EMG Relaxation Training with Hyperkinetic Children: A Behavioral Alternative"
Stephen E. Breuning (Oakdale Center for Developmental Disabilities) "A Comparison of DRO, Token Economy, and Response-Cost Procedures as Behavioral Alternatives to Drug Control with Hyperkinetic Elementary School Students and Institutionalized Retardates"
Travis Thompson (University of Minnesota) "Comparison of Behavior Modification Procedures and Tranquilizing Drugs in the Treatment of Institutionalized Adult Retardates"

10:00–12:00 / SAN JUAN ROOM
Symposium 49 / Behavior Analysis in Community Mental Health; Or, A Funny Thing Happened on the Way to Changing the World
Chair: Beverly Johnson (Southern Illinois University)
Discussant: Grace Poppen (Southern Illinois University)
Participants:
Beverly Johnson (Southern Illinois University) "Client Data Collection"
Ron Sipko (Southern Illinois University) "Behavioral Assessment"
Vicki Veitch (Southern Illinois University) "Mental Health Involvement in Academic Behavior"
Grace Poppen (Southern Illinois University) "A Behavioral Analysis of Problems and Issues Confronting Single Parents"

10:00–1:00 / CARACAS ROOM
Symposium 50 / The Behavior Analyst as Consultant to Business: Applying Tools of the Trade
Chair: Twila Johnson (Behavioral Systems, Inc., Atlanta, GA)

February 7, 1987

Lorraine B. Torres, Director
Division of Extramural Activities, NIMH
Room 9-105, Parklawn Building
5600 Fishers Lane
Rockville, Maryland 20857

Vicky J. Davis
12 Bethany Drive
Pittsburgh, PA 15215

Dear Ms. Torres:

Thank you for the opportunity to respond to the preliminary report of the investigatory panel. My comments will be brief.

On page 24 and later in an Appendix, the panel seems to have misunderstood some comments that I made or I misunderstood the question. Nevertheless, please let me clarify. The Davis, Poling, Wysocki, and Breuning (1981) article and the thesis contain no irregularities. The study was conducted and reported accurately.

In discussing this with the panel I meant to say that there were no drug manipulations for research purposes and that placebos were certainly used. Regardless of what the Coldwater administration has stated, placebos were used at Coldwater (as the panel has confirmed) and I have never seen a Coldwater policy which addressed the issue of placebos.

Additionally, upon completion of the study a written copy of the prepublication draft and my thesis were reviewed by each coauthor, the Coldwater Research Committee, Western Michigan University Faculty, Dr. Sprague, and Mr. Rogan the Coldwater Facility Director. No one ever raised a single concern over the issue of placebos. Placebo use is clearly identified in the manuscript and thesis copy they reviewed. A copy of Dr. Sprague's and Mr. Rogan's letters are enclosed.

Again, I wish to repeat that there are no irregularities in the conduct or reporting of this study.

Sincerely,

Vicky J. Davis

Vicky J. Davis

Enclosures

University of Illinois at Urbana-Champaign

College of Education
INSTITUTE FOR CHILD BEHAVIOR AND DEVELOPMENT

51 Gerty Drive
Champaign, Illinois 61820

December 4, 1980

Ms. Vicky Davis
5103 Merryview Drive
Kalamazoo, Michigan 49008

Dear Vicky:

I read your thesis and enjoyed it. Enclosed are copies of the pages where I had comments.

Best of luck on publishing it. Perhaps a trend will be set to study effects of antiepileptics on learning performance.

Sincerely,

Bob

Robert L. Sprague, Ph.D.
Director

RLS/sb
Enclosure

matching to sample performance of each person was tested at each dose level is shown later in Figure 1. DPH/serum levels and EEG assessments were completed prior to baseline (Session 1) and the final dose reduction (Sessions 13, 42, and 55 for Subjects D, L, and E, respectively). Subjects L and E received an additional DPH/serum level and EEG assessment four days after the onset of the 150 mg dose (Sessions 22 and 30, respectively). Routine Regional Center seizure monitoring procedures were in effect throughout the study. Double-blind procedures were used, as neither the ward staff nor the subjects were aware of the DPH dose or whether a placebo was being used.

STATE OF MICHIGAN
WILLIAM G. MILLIKEN, Governor
DEPARTMENT OF MENTAL HEALTH
FRANK M. OCHBERG, M.D. DIRECTOR
**Coldwater Regional Center
For Developmental Disabilities**
P.O. Box 148, Coldwater, Michigan 49036
Telephone 517/279-9551

December 5, 1980

Vicky June Davis
Research Services
Coldwater Regional Center
P.O. Box 148
Coldwater MI 49036

Dear Vicky:

Thank you for sharing your thesis with me. I wish you all the luck in the University review of this fine work.

Sincerely,

Robert L. Rogan
Facility Administrator

RLR:ra

University of Illinois
at Urbana-Champaign

**Institute for Child Behavior
and Development**

51 Gerty Drive
Champaign
Illinois 61820

College of
Applied Life Studies

February 9, 1987

Director Lorraine B. Torres
Division of Extramural Activities, NIMH
Room 9-105, Parklawn Building
5600 Fishers Lane
Rockville, MD 20857

Dear Mrs. Torres:

This letter is in response to the NIMH draft report on Dr. Stephen E. Breuning.

I request that this letter be made part of the public documents to be released whenver the report is finally issued.

Comments

1. I note that although NIMH took 3 years and 23 days to issue the draft report (from December 20, 1983 when I first wrote my letter of alleged misconduct to January 12, 1987), NIMH only allows less than 1 month (January 12, 1987 to February 10, 1987) for people to respond to the document.

2. There is no timetable of the major events in this investigation which makes it very difficult for the reader to appreciate how long various activities took in the investigation. Therefore, I enclose such a timetable.

Date	Item	Time from start
12/20/83	Sprague's letter to NIMH	0
01/17/84	Torres' letter to U of Pittsburgh	28 days
08/23/84	Silver's letter announcing appointment of Mr. James Schriver as investigator	8 months 3 days
10/15/84	First interview by Schriver	9 months 26 days
02/15/85	Torres' letter announcing appointment of Panel	1 yr 1 month 26 days
04/19/85	First interview by Panel	1 yr 3 months 30 days
01/12/87	Draft report	3 yrs 23 days

3. I am still greatly concerned about the welfare of mentally retarded people taking psychotropic drugs whose physicians may be influenced by Dr. Breuning's extensive publications. I wrote about these concerns to Mr. Schriver December 6, 1984 and Dr. Friedhoff April 25, 1985, and I received no reply to either letter. Since the draft report contains no recommendations as to possible actions, will the editors of all the journals in which Dr. Breuning's articles appeared be directly notified as to the findings? Will the report be released to the media?

4. I received a telephone call from Mrs. Torres on January 5, 1984 (documented by my memo to Dean Theodore L. Brown on January 5, 1984) in which she indicated that the University of Pittsburgh would be given 100 days to report back to NIMH on the results of their investigation. Since this investigation has been delayed substantially by the University of Pittsburgh's initial refusal to investigate Dr. Breuning's research while at the University of Pittsburgh, what happened to this 100-day deadline? It is noted in the draft report that "NIMH indicated that it would wait for the report [italics added] of the investigation before deciding on Institute action," (page 3 of draft report) implying that there was no deadline of any kind imposed the University of Pittsburgh.

5. It is amazing that in the Panel's 32-page report there is no mention of one of the most important facts obtained in this investigation. The University of Pittsburgh obtained early in their investigation Dr. Breuning's actual confession of falsification. This fact is documented in the Adler, Michaels, and Lee letter of February 17, 1984 which stated, "Dr. Breuning admitted to us that statements in the abstract were false [italics added]."

It is only reasonable that such a confession should have triggered some kind of disciplinary action by the University of Pittsburgh. Nevertheless, in Dr. Leon's letter to Mrs. Torres of July 6, 1984, he states, "our Hearing Board can find *no serious fault with Dr. Breuning's activities here at Pittsburg* [italics added]."

This denial of their own committee evidence continued as stated in Dr. Silver's, Acting Director of NIMH, letter to me of August 23, 1984. The letter states "The University [of Pittsburgh] has informed the National Institute of Mental Health (NIMH) that *it has no grounds to take action against Dr. Breuning relative to his activities while a member of its faculty* [italics added]."

6. I note the great similarity between Appendix I Analyses of Publications in the draft report and the material I sent to Mr. Schriver on January 9, 1985 before the Panel was appointed. This material was entitled Comments on Research of Stephen E. Breuning and contained Tables 1, 2, 3, and 4 which analyzed Dr. Breuning's articles and the large number of problems with them. In this context it should also be noted that on the last day of Mr. Schriver's visit to me, December 7, 1984, I had given him 571 pages of documentation. Subsequently, I sent him considerably more documentation to him. Earlier on May 2, 1984, the reprints of Dr. Breuning's I had sent to NIMH was acknowledged in a letter from Mrs. Torres.

7. Nowhere in draft report is the issue of possible plagiarism mentioned although I provided Mr. Schriver with a letter Dr. Mary K. Walker wrote to Mr. Payne Thomas of Charles C Thomas publisher about this issue. The possible plagiarism was in Dr. Breuning's article published in *Clinical Psychology Review*, 1982, *2*, 79-114. It is further noted that Mr. Schriver interviewed Dr. Walker on January 14, 1985.

8. There are problems with balance in the draft report. I am criticized for "failure to adequately oversee the subcontract" at the University of Pittsburgh. I point out that this involved oversight from the Champaign-Urbana, Illinois which is about 500 miles away from Pittsburgh and involves the operation of another university. Yet, in the same draft report *not one word is mentioned* of the fact that a University of Pittsburgh committee obtained a confession of falsification. Subsequently, the University of Pittsburgh denied it had any grounds to take action against Dr. Breuning while he was a faculty member there. This is a case, to cite a Biblical analogy, of the Panel observing the speck that is in one person's eye while ignoring the much larger beam (of timber) that is in another person's eye.

Sincerely yours,

Robert L. Sprague

Robert L. Sprague

cc: Professor Theodore L. Brown
Associate Dean Elaine J. Copeland

University of Illinois
at Urbana-Champaign

Graduate College

107 Coble Hall
801 South Wright Street
Champaign, IL 61820

February 5, 1987

Dr. Frank J. Sullivan
Deputy Director
National Institute of Mental Health
Alcohol, Drug Abuse,
and Mental Health Administration
Rockville, MD 20857

Dear Dr. Sullivan:

This letter constitutes the response of the University of Illinois to the preliminary report of the committee appointed by the National Institutes of Mental Health to investigate allegations of scientific misconduct by Stephen E. Bruening.

The University of Illinois wishes to commend the panel for a very thorough, forthright and courageous report. As in all matters of this kind, the amount of work required to obtain a clear picture of what has occurred, and to arrive at an appropriate judgment is immense. The scientific community is indebted to the panel for the commitment of time and energy required to complete the report.

We wish to comment on two general aspects of the panel's conclusions:

1. Conclusions regarding the role of the University of Illinois

The panel concluded that, "the University of Illinois failed to conduct a thorough investigation. The committee appointed to look into the matter based its finding on secondary evidence provided by a single source, Dr. Sprague. The committee's findings were that Dr. Sprague had behaved appropriately in reporting his suspicions of Dr. Bruening's research and that Dr. Bruening's work did not impact on Dr. Sprague's research. While the University of Illinois committee found that there was cause to believe that Dr. Bruening had engaged in scientific misconduct, they did not pursue this."

In response it is important to clarify the appropriate role for the University of Illinois in this matter. Dr. Sprague's suspicions regarding Dr. Bruening were brought to the attention of the Office of the Vice Chancellor for Research at an early stage. (At that time the Institute for Child Behavior and Development was a Special Unit of the Graduate College, under the Graduate Dean and Office of the Vice Chancellor for Research.) Upon receipt of Dr. Sprague's letter detailing his concerns regarding Dr. Bruening's work, we quickly appointed the ad hoc committee described in the panel's report. In considering an appropriate charge for this committee it should be kept in mind that Dr. Sprague is the only person involved in this affair who was a University of Illinois faculty member. Secondly, none of the studies called into question were conducted on this campus, or at sites related to the University of Illinois. Thirdly, there are no faculty on this campus, including medical faculty, whose research interests are closely related to the areas involved in the alleged misconduct.

For all of these reasons, we felt that our obligation consisted in reporting the alleged misconduct to NIMH, which was done, and to carry out an investigation as thorough as we could make it, of Dr. Sprague's role, if any, in the research being called into question, and of his relationship to Dr. Bruening. The committee appointed for that purpose consisted of three distinguished faculty with experience in human subject research. We believe this committee performed commendably, and covered as thoroughly as it could that ground which was appropriate to us.

As to the statement of the panel that the University did not pursue its finding that there was cause to believe that Dr. Bruening had engaged in scientific misconduct, we believe that statement to be inaccurate. In the first place, the suspicions of Dr. Bruening's misconduct had already been reported to NIMH, and we knew that the University of Pittsburgh had been alerted to our suspicions. Secondly, we forwarded the report of our ad hoc committee to NIMH in a timely manner. That report lent substance to Dr. Sprague's suspicions of Dr. Bruening's work, and thus should have helped confirm the need for additional investigation. Finally, it should be noted that the Office of the Vice Chancellor for Research and Dr. Sprague cooperated fully with Mr. Schriver in his subsequent investigations of the matter. Mr. Schriver spent many days at the University of Illinois. During that time he enjoyed the full cooperation of Dr. Sprague and campus administration in conducting his investigation. Thus, we feel that we did all that we had it in our power to do to further the investigation into Dr. Bruening's research activities. I should note finally that at no time following submission of our ad hoc committee report to NIMH did we receive any indication, verbally or in writing, that we had fallen short in any respect in our efforts to cooperate fully in the investigation. In fact, I recall making several telephone calls to Ms. Torres to inquire as to what we might do further to move the investigation along more quickly. For the most part I was unable to reach Ms. Torres.

2. Conclusions regarding Dr. Sprague's role

I am sure that the members of the panel are well aware of the personal anguish this affair has caused Dr. Sprague. As the person to whom Dr. Sprague reported administratively, and as his friend, I can report that the cost to him in emotional stress has been great. Further, the time required on his part to cooperate fully in the investigation, and to pursue the matter to its conclusion has been continuing and severe. In the wake of the panel's discovery of wholesale malfeasance on Dr. Bruening's part, across several years, and in a variety of contexts, it is easy enough to assert that Dr. Sprague should have exerted a more rigorous oversight of the subcontract at the University of Pittsburgh under Grant MH-32206.

However, it is normal practice in science to assume integrity and competence on the part of one's colleagues, absence evidence to the contrary. Thus, until Dr. Sprague's suspicions were aroused, there was little reason for him to have more than the usual communication between collaborating colleagues. The panel surely understands the natural reluctance any of us have to come to the conclusion that a colleague has falsified research results. It is an unfortunate fact that someone deliberately falsifying research results generally enlists others in the falsification, albeit often unwillingly and unwittingly. Dr. Sprague exercised sound judgment and courage in discerning and calling attention to the irregularities in Dr. Bruening's work. His continued pursuit of this matter is, in our judgment, praiseworthy. In the absence of specific suggestions as to how Dr. Sprague might reasonably have more adequately overseen the sub-contract at the University of Pittsburgh, we believe that there is not a basis for this statement in the findings of the panel.

Sincerely,

Theodore L. Brown

Theodore L. Brown
Former Dean of the Graduate College and
Former Vice Chancellor for Research
(September, 1980 to August, 1986)
Current Acting Director of the Beckman
Institute

The above response represents the response of the University of Illinois.

Thomas E. Everhart

Thomas E. Everhart
Chancellor

Judith S. Liebman

Judith S. Liebman
Acting Vice Chancellor for Research and
Acting Dean, The Graduate College

cc: R. M. Berdahl, B. H. Higgins, S. O. Ikenberry, M. W. Weir

Summary

Report of Investigation of Alleged Scientific Misconduct

The National Institute of Mental Health (NIMH) has completed an exhaustive investigation of allegations of scientific misconduct against Dr. Stephen E. Breuning in connection with two NIMH research grants. Dr. Breuning's reported work under these grants centered on the effects of neuroleptic and stimulant drugs on the behavior of the mentally retarded. The attached report documents in detail the information considered and the process followed by an investigative panel of senior scientists, convened by NIMH, in arriving at their central conclusion that Dr. Breuning repeatedly and over a long period of time engaged in serious scientific misconduct.

Background

Concerns about Dr. Breuning's work were brought to the attention of NIMH in December 1983, by Dr. Robert L. Sprague, Director, Institute for Child Behavior and Development, University of Illinois at Urbana-Champaign, and principal investigator on grant MH-32206 for research to assess tardive dyskinesia in retarded populations. Dr. Sprague gave two examples of work being reported by Dr. Breuning which he regarded as unsupportable: an abstract of a paper Dr. Breuning had intended to present at a scientific meeting and a progress report Dr. Breuning had shown him on grant MH-37449, on which Dr. Breuning was principal investigator, awarded to the University of Pittsburgh for research on stimulant drug use with mentally retarded children.

Dr. Sprague was introduced to Dr. Breuning in 1978. In 1979, when administrative problems in Illinois made it impossible to continue work under his own research grant at his originally selected field research sites, Dr. Sprague moved one of the sites to the Coldwater Regional Center, Coldwater, Michigan, where Dr. Breuning was then employed. He named Dr. Breuning as his consultant and liaison there. Ms. Vicky Davis was appointed as a project staff member at Coldwater with her salary paid directly by the University of Illinois from Dr. Sprague's grant.

In his grant progress reports, Dr. Sprague reported studies at Coldwater and listed publications on which Dr. Breuning was author, or a coauthor.

After Dr. Breuning moved to the University of Pittsburgh in January 1981, Dr. Sprague negotiated a subcontract under his grant with the University of Pittsburgh which allowed Dr. Breuning to continue as a collaborator.

Through the University of Pittsburgh, Dr. Breuning applied for, and on July 1, 1982, received a research grant for 2 years to examine appropriate dose levels of stimulant drugs in the treatment of 48 hyperactive mentally retarded children admitted to the John Merck Program of the Western Psychiatric Institute and Clinic (WPIC) there. In his first progress report on this grant, Dr. Breuning stated that 65 percent of the subjects under one study and 35 percent of the subjects under a second study had completed the protocols.

An application for 4 years of additional support under this grant was received by NIMH October 1, 1983. In the progress report included in that application, Dr. Breuning stated that 6 studies had been completed and a seventh nearly completed. He listed 11 scientific articles reporting on his work as published, in press, or in preparation. That application was later withdrawn by Dr. Breuning.

University Investigations

At Dr. Sprague's request, a committee was formed at the University of Illinois to carry out an investigation. On April 9, 1984, the committee reported that there was a reasonable basis for suspecting fraudulent scientific practice by Dr. Breuning; that there was reasonable cause for a thorough investigation which the committee assumed would be carried out by the University of Pittsburgh; and that there was no evidence of complicity by Dr. Sprague or other University of Illinois faculty or staff, that Dr. Sprague's research data were independent of those of Dr. Breuning, and that Dr. Sprague had exercised reasonable diligence and behaved appropriately in notifying NIMH of his concerns.

The University of Pittsburgh was notified by NIMH of the allegations against Dr. Breuning on January 17, 1984. The university had already initiated an investigation based on Dr. Sprague's expressed concerns. Committees in the Department of Psychiatry and the School of Medicine reported that Dr. Breuning's research written or published while he was at Coldwater contained significant irregularities and could not be supported by the data. The latter committee recommended a formal investigation which was undertaken. Despite an initial and repeated request by NIMH that Dr. Breuning's research while at Pittsburgh be investigated, both committees were charged only with reviewing Dr. Breuning's work reported while he was at Coldwater. The third investigative committee, a University hearing board, reported that because Dr. Breuning had by then resigned from the University of Pittsburgh, its charge was limited to determine whether or not there had been misuse of NIMH funds. That board found no such misuse.

In August 1984, NIMH notified Dr. Breuning, Dr. Sprague, and the two universities that, because of unresolved issues, it would conduct a comprehensive investigation. After NIMH had undertaken its investigation, a fourth investigative committee was established at the University of Pittsburgh, by the Department of Psychiatry. That Ad Hoc Committee, chaired by the late Dr. Robert Miller, expanded its charge, conducted an exhaustive investigation, and concluded that the work Dr. Breuning reported under his research grant could not have been done at WPIC.

NIMH Investigation

In January 1985, NIMH established a panel of five distinguished senior scientists to conduct a comprehensive investigation of the allegations against Dr. Breuning:

Arnold J. Friedhoff, M.D., Chairman
Professor of Psychiatry and
Director of Millhauser Laboratories
New York University School of Medicine

C. Keith Conners, Ph.D.
Director of Research, Department of Psychiatry
Children's Hospital National Medical Center
Washington, D.C.

Richard I. Shader, M.D.
Professor and Chairman, Department of Psychiatry
Tufts University School of Medicine
Psychiatrist-in-Chief
New England Medical Center
Member, National Advisory Mental Health Council

Herbert G. Vaughan, Jr., M.D.
Director, Rose F. Kennedy Center for Research
in Mental Retardation and Human Development
Professor of Neuroscience, Neurology and Pediatrics
Albert Einstein College of Medicine

Edward F. Zigler, Ph.D.
Sterling Professor, Department of Psychology
Yale University

Materials were gathered by NIMH staff and a consultant investigator and preliminary interviews conducted at Coldwater and Pittsburgh. The Panel held its first meeting March 12, 1985. The Panel met 9 times and individual members met numerous times with NIMH staff. The Panel conducted extensive interviews, including a meeting of the full Panel with Dr. Breuning.

Dr. Sprague, Ms. Davis, all major coauthors of Dr. Breuning, and research, administrative, and clinical staff at Coldwater and Pittsburgh who reasonably could have had knowledge of this research were interviewed by the full Panel or by Panel members. In all, 74 interviews were conducted during the course of the investigation, including interviews with those whom Dr. Breuning named in his meeting with panel members as knowledgeable of his work. Panel members visited Coldwater and Pittsburgh and a consultant investigator visited Oakdale. The Panel and staff analyzed in detail the contents of 25 publications and reports authored or coauthored by Dr. Breuning, as well as his grant applications and progress reports.

The work of the Panel was complicated by Dr. Breuning's shifting, and often contradictory explanations as to the sites of the reported research. Aside from his grant applications and progress reports, the site of research reported was identified in only two of the publications examined, and Dr. Breuning later disavowed one of these identifications. The Panel originally assumed that the research had been done at the Coldwater Regional Center and the University of Pittsburgh, the places of Dr. Breuning's employment during the period when the reports and publications were prepared and appeared. Dr. Breuning admitted that he had done none of the research at the University of Pittsburgh and attributed it to the Coldwater Regional Center, the Oakdale Regional Center, schools in the Chicago area, and various sites in Illinois.

NIMH Panel's Conclusions

The Panel arrived at the following central conclusion regarding Dr. Breuning:

> It is the unanimous conclusion of the Panel that Stephen E. Breuning knowingly, willfully, and repeatedly engaged in misleading and deceptive practices in reporting results of research supported by or citing Public Health Service grants MH32206 and MH37449; that he did not carry out the described research; and that only a few of the experimental subjects described in publications and progress reports were ever studied; and that the complex designs and rigorous methodologies reported were not employed. Dr. Breuning misrepresented, implicitly or explicitly, the locations at which research was supposedly conducted. The Panel did not find credible Dr. Breuning's shifting explanations as to where the various studies were carried out and his ultimate contention that many were conducted years before in the Chicago area. The Panel unanimously concluded, on the basis of all the facts, that Dr. Stephen E. Breuning has engaged in serious scientific misconduct.

The Panel also noted that Dr. Breuning's work "made a strong impression on the mental retardation field with a small number of publications in which he described well-designed studies that produced relatively robust and straightforward findings," and that "Dr. Breuning appears publicly, giving addresses in which he uses his publications to support his recommendations on social policy and treatment practices."

Regarding Ms. Vicky Davis, the Panel concluded:

> Ms. Davis was first author on two studies, one of which the Panel found to involve significant irregularities and the second of which the Panel found not to have been carried out as described.

The Panel concluded that Ms. Davis did not behave in a scientifically responsible manner in that she either was, or should have been, aware of improper reporting of data and methods.

The Panel did not investigate other coauthors in depth. The Panel did note that their interviews revealed a pattern of Dr. Breuning inducing others, who sometimes had little actual involvement with the research, into coauthorship; of major coauthors who had not examined the primary source data, or raw data, for these studies; and of individuals whose names were added to manuscripts without their knowledge. The Panel found "no evidence of knowing participation in scientific misconduct in its limited review of the activities of other coauthors."

The Panel commended Dr. Sprague for bringing his concerns about Dr. Breuning's work to the attention of NIMH. They did "question Dr. Sprague's judgment in uncritically including Dr. Breuning's publications, on which he was himself not a coauthor, in his grant progress reports." They also expressed concern about Dr. Sprague's "failure to adequately oversee the subcontract" to the University of Pittsburgh.

The Panel concluded that neither university "adequately fulfilled" its obligation to diligently pursue allegations of scientific misconduct. While both universities had committees which found indications of scientific misconduct on Dr. Breuning's part, neither conclusively pursued these. After NIMH had begun its investigation, the Department of Psychiatry of the University of Pittsburgh established another committee which broadened its charge and conducted an exhaustive review of Dr. Breuning's work at the university. This committee was commended by the Panel.

NIMH Panel Recommendations

Specific Panel recommendations included:

- debarrment of Dr. Breuning for the maximum period of time from receiving Public Health Service funds
- referral of grant applications and progress reports for MH-37449 to the Department of Justice with a recommendation that prosecution of Dr. Breuning be considered
- notification of panel findings to the Universities of Illinois and Pittsburgh, officials at other alleged research sites, Dr. Breuning's present employer, Dr. Breuning's coauthors, editors of journals and publishers of books in which articles reviewed by the Panel appeared, relevant professional associations, licensing and certifying bodies, and State agencies responsible for care of the mentally retarded
- general publication of the Panel findings to counteract the effect of unpublished research reports

The Panel also made general recommendations concerning responsibility of coauthors and editors for publications and presentations; responsibility of principal investigators and grantee institutions; and procedures for future investigations.

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SUMMARY OF THE ADAMHA ADMINISTRATOR'S DECISIONS IN RESPONSE TO THE INVESTIGATIVE REPORT ON DR. STEPHEN E. BREUNING

1. Recommend to the Secretary, HHS that Dr. Breuning be debarred from eligibility for HHS financial assistance and contracts for a period of 10 years.

2. Refer the Panel report, along with grant applications and progress reports for MH37449, to the Department of Justice with a recommendation that prosecution of Dr. Breuning be considered.

3. Prohibit Dr. Breuning from serving as a member or consultant to any ADAMHA public advisory group for a ten year period.

4. Request that NIMH initiate action for recovery of funds under grant MH37449 and under the subcontract to the University of Pittsburgh from grant MH32206.

5. Send copies of the Panel's report to the University of Illinois and University of Pittsburgh calling their attention to the Panel's observations about their investigations.

6. Send copies of the Panel's report to Dr. Breuning's current employer, relevant professional associations and licensing or certifying bodies, State agencies responsible for the care of the mentally retarded, all coauthors of Dr. Breuning's publications reviewed in the Panel`s report, journals which published articles mentioned in the report, organizations of scientists working in the field of mental retardation and groups representing the mentally retarded.

7. Provide the Panel's report to reviewing and deciding officials for their information and consideration in the event that Ms. Vicky Davis submits a grant application to ADAMHA within the next two years.

8. Send a copy of the report to Dr. Sprague and notify him of concurrence with the Panel's expression of concern, as well as their commendation for reporting the alleged scientific misconduct.

9. Recommend issuance of a press release on this report.